Pulmonary function and cardiorespiratory fitness in idiopathic Parkinson's disease

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Abstract

Idiopathic Parkinson's disease (IPD) is a progressive neurodegenerative disorder, secondary to dopaminergic depletion, which primarily affects motor control via the basal ganglia. It is a multi system disease affecting dopaminergic neurones throughout the body. The Parkinsonian syndromes are associated with excess morbidity and mortality from respiratory causes. Pulmonary function studies have yielded conflicting results in IPD. There is a lack of high quality research examining the effect of exercise on pulmonary function and aerobic capacity in IPD. Understanding the pattern of any respiratory dysfunction and impairment in cardiorespiratory fitness in IPD, and interventions that could modify these, are of importance in dyspnoea, hypoxia, hypercapnia, pneumonia, speech, swallowing, sleep disordered breathing, daytime somnolence, acute respiratory failure, extubation difficulties, increased respiratory infections and reduced exercise tolerance and functional capacity.

We recruited 103 individuals with IPD, at different disease stages, from the Northumbria Parkinson's Disease Service to define the pattern of pulmonary dysfunction and respiratory muscle strength. 100 participants completed a cross-sectional study comprising demographics, questionnaires and comprehensive pulmonary function testing, including spirometry, flow volume loops, lung volume assessment and respiratory muscle strength testing. Of these 100, 32 volunteered for a randomised control trial (RCT) with additional measurements of aerobic capacity, assessed by cardiopulmonary exercise testing, and exercise capacity, assessed by six minute walk testing. The participants were randomised, 1:1, control:intervention. The intervention group participated in a 12 week, 3 times weekly, exercise intervention. The baseline assessments were repeated in both groups immediately after the intervention, with 27 completing the RCT.

The cross-sectional pulmonary function study revealed an increased prevalence of obstructive spirometry, upper airway obstruction and inspiratory muscle weakness in this population. The randomised control trial demonstrated statistically significant improvements in the intervention group only in; aerobic capacity, exercise capacity, subjective parkinsonian symptoms, quality of life, depression, anxiety, sleep and sleepiness.

Dedication

For everyone affected by Parkinson’s

Acknowledgements

I would like to express my sincere gratitude to everyone who has been involved with the study. I would like to thank my supervisors, Professor Richard Walker and Professor Michael Trenell, for their enthusiasm, support, guidance and patience. I would also like to thank Keith Gray, who provided very welcome advice on statistical analysis. Sincere thanks go to the entire Northumbria Parkinson's disease team, but in particular Parkinson's specialist nurses Karen Ullyart and Catherine Jones, who dedicated a large amount of time and effort to recruitment and assessment for the study. Thanks also go to Djordje Jakovljevic and Sarah Moore of the Movelab for their knowledge and assistance, and Dr Stephen Bourke of Northumbria Healthcare for his knowledge and advice. Sincere thanks also go to the Northumbria lung function department, led by Helen Morrow, for their expert assessments and flexibility. Personally, and from the participants in the randomised control trial, I would like to thank the Healthy Living Centre staff, led by Maureen Turner, for their enthusiastic, friendly, safe and welcoming delivery of the exercise intervention. Vitally I would like to express my sincere gratitude to the patients who willingly and generously gave their time and enthusiasm to participate in this research, I have met amazing and inspiring people affected by Parkinson's during this study and you have taught me a huge amount.

Finally I would like to thank my family; my mother, Sue, my brother, Carey, and my late father, Peter, for their unconditional love, support and encouragement which has got me to where I am today and to my wonderful husband, Christopher, I will never be able to thank you enough for your love, support, encouragement and patience. I am so very grateful, thank you.

Publications and presentations

Publications

A.K. O'Callaghan, D.G. Jakovljevic, M.I. Trenell, R.W. Walker. The effect of an exercise intervention on aerobic capacity in idiopathic Parkinson's disease. Movement Disorders 2014; 29 S1: S255.

A.K. O'Callaghan, D.G. Jakovljevic, M.I. Trenell, R.W. Walker. The effects of an exercise intervention on cardiovascular system and skeletal muscle function in idiopathic Parkinson's disease. Movement Disorders 2014; 29 S1: S255.

O'Callaghan A, Jakovljevic D, Trenell M, Walker R. Maximum heart rate in idiopathic Parkinson's disease. Abstract Book 20th World Congress on Parkinson's Disease and Related Disorders, Geneva, Switzerland, December 8-11, 2013; no. 081: page 26.

O'Callaghan A, Walker R. First-degree atrioventricular block in idiopathic Parkinson's disease. Abstract Book 20th World Congress on Parkinson's Disease and Related Disorders, Geneva, Switzerland, December 8-11, 2013; no. 084: page 27.

O'Callaghan A, Walker R. Electrocardiographic artefact in idiopathic Parkinson's disease. Abstract Book 20th World Congress on Parkinson's Disease and Related Disorders, Geneva, Switzerland, December 8-11, 2013; no. 082: page 26.

White R, O'Callaghan A, van Hees V, Gray W, Jakovljevic D, Trenell M, Walker R. The relationship between aerobic capacity, exercise capacity and physical activity in idiopathic Parkinson's disease. Abstract Book 20th World Congress on Parkinson's Disease and Related Disorders, Geneva, Switzerland, December 8-11, 2013; no. 279: page 77.

Presentations

2015 Platform presentation - Exercise and cardiorespiratory function in idiopathic Parkinson’s disease. British Geriatric Society Movement Disorders Section Meeting, Birmingham.

2014 Poster presentation - A randomised control trial of structured exercise therapy on quality of life, sleep and mood in Parkinson’s. Parkinson’s UK research conference, York.

2014 Poster presentation - The effect of an exercise intervention on aerobic capacity in idiopathic Parkinson’s disease. 18th International Congress of Parkinson's Disease and Movement Disorders, Stockholm, Sweden.

2014 Poster presentation - The effects of an exercise intervention on cardiovascular system and skeletal muscle function in idiopathic Parkinson’s disease. 18th International Congress of Parkinson's Disease and Movement Disorders, Stockholm, Sweden.

2014 Platform presentation - The effect of an exercise intervention on cardiopulmonary outcome measures in idiopathic Parkinson’s disease. Three Rivers Parkinson’s meeting, Durham.

2013 Platform presentation - Maximum heart rate in idiopathic Parkinson’s disease. XX World Congress on Parkinson’s Disease and Related Disorders, Geneva, Switzerland.

2013 Poster presentation - First-degree atrioventricular block in idiopathic Parkinson’s disease. XX World Congress on Parkinson’s Disease and Related Disorders, Geneva, Switzerland.

2013 Poster presentation - Electrocardiographic artefact in idiopathic Parkinson’s disease. XX World Congress on Parkinson’s Disease and Related Disorders, Geneva, Switzerland.

2013 Poster presentation - The relationship between aerobic capacity, exercise capacity and physical activity in idiopathic Parkinson's disease. XX World Congress on Parkinson's Disease and Related Disorders, Geneva, Switzerland.

Statement of work undertaken

Previous training in respiratory medicine, prior to geriatric medicine with a specialist interest in movement disorders, fostered my interest in pulmonary function and cardiorespiratory fitness in this group. I devised the concept for the study. The design of both parts of the study, cross-sectional and randomised control trial, was collaborative between myself and with input from my supervisors, Professor Walker and Professor Trenell. The funding for the project was applied for by myself from Parkinson's UK and The British Geriatrics Society and awarded in the forms of an innovation grant and a SpR start up grant respectively. I applied for ethical approval and attended the Research Ethics Committee with Professor Walker.

I oversaw the running of the cross-sectional and randomised control trial sections of the study. The assessment visits were conducted by either myself or one of the Northumbria Parkinson's specialist nurses. The pulmonary function testing was performed by the Pulmonary Function Department at North Tyneside General Hospital. All testing was performed by qualified, experienced respiratory physiologists accredited to the Association for Respiratory Technology and Physiology (ARTP). The cardiopulmonary exercise testing was performed by myself accompanied by either an exercise physiologist or physiotherapist. The exercise intervention was supervised by Moor Park Healthy Living Centre (HLC) staff (trained to British Association of Cardiac Rehabilitation level 4 and GP referral qualification level 3) and frequently myself also.

Processing and analysis of data was my own work. Statistical analysis was undertaken by myself, with invaluable advice from Keith Gray.

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Abbreviations

ABG = Arterial blood gas

ALS = Amyotrophic lateral sclerosis

ANS = Autonomic nervous system

ARTP = Association for Respiratory Technology and Physiology

ATS = American Thoracic Society

a-vO2 diff = Arterial-venous oxygen difference

BDNF = Brain derived neurotrophic factor

BMI = Body Mass Index

BTS = British Thoracic Society

cmH_2O = cm water pressure

CBD = Corticobasal degeneration

CO = Carbon monoxide

CO_2 = Carbon dioxide

COMT = Catechol-O-methyl transferase

COPD = Chronic obstructive pulmonary disease

CPET = Cardiopulmonary exercise test

CT = Computed tomography

DBP = Diastolic blood pressure

DLB = Dementia with Lewy bodies

DLCO = Diffusing capacity of the lung for carbon monoxide

ECCS = European Community for Coal and Steel

ECG = Electrocardiogram

ERS = European Respiratory Society

ERV = Expiratory reserve volume

FBC = Full blood count

FEF = Forced expiratory flow

FEV = Forced expiratory volume

FEV1 = Forced expiratory volume in one second

FH = Family history

FIF = Forced inspiratory flow

FRC = Functional residual capacity

FVC = Forced vital capacity

HADS = Hospital Anxiety and Depression Scale

Hb = Haemoglobin

He = Helium

HIT = High intensity interval training

HLC = Healthy Living Centre

HR = Heart rate

IC = Inspiratory capacity

ICD = Impulse control disorders

IPD = Idiopathic Parkinson’s disease

IRV = Inspiratory reserve volume

ITGV = Intrathoracic gas volume

IVC = Inspiratory vital capacity

KCO = Transfer coefficient

kPa = kilopascal

LBs = Lewy bodies

LLN = Lower limit of normal

LNs = Lewy neurites

LRRK2 = Leucine rich repeat kinase 2

MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale

MEF = Maximum expiratory flow

MEP = Maximal expiratory pressure

MET = Metabolic equivalent

MG = Myasthenia gravis

MIF = Maximum inspiratory flow

MIP = Maximal inspiratory pressure

MMEF = Maximum mid expiratory flow

MMSE = Mini mental state examination

MND = Motor neuron disease

MoCA = Montreal Cognitive Assessment

MPPP = Desmethylprodine 1,3-Dimethyl-4-phenyl-4-propionoxypiperidine

MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

MRI = Magnetic resonance imaging

MS = Multiple sclerosis

MSA = Multiple system atrophy

MVV = Minute ventilatory volume

N_2 = Nitrogen

NICE = National Institute for Health and Care Excellence

NIV = Non-invasive ventilation

OSA = Obstructive sleep apnoea

O_2 = Oxygen

P_{sniff} = Sniff nasal inspiratory pressure

PaO_2 =Partial pressure of oxygen

$PaCO_2$ = Partial pressure of carbon dioxide

PCF = Peak cough flow

PD = Parkinson's disease

PDQ-39 = Parkinson's Disease Questionnaire

PDSS = Parkinson's Disease Sleep Scale

PE_{max} = Maximal expiratory pressure

PEF = Peak expiratory flow

PFT = Pulmonary function test

PI_{max} = Maximal inspiratory pressure

PIF = Peak inspiratory flow

PIGD = Postural instability gait difficulty

PINK1 = PTEN-induced putative kinase 1

PMH = Past medical history

PSP = Progressive supranuclear palsy

Q_T = Cardiac output

R_{AW} = Airway resistance

RCT = Randomised control trial

RBD = REM sleep behaviour disorder

REM = Rapid eye movement

RMW = Respiratory muscle weakness

RV = Residual volume

SBP = Systolic blood pressure

SH = Social history

SMR = Standardised mortality ratio

SNc = Substantia nigra pars compacta

SNCA = α-Synuclein

SNIP = Sniff nasal inspiratory pressure

SPECT = Single-photon emission computed tomography

SV = Stroke volume

SVC = Slow vital capacity

TD = Tremor dominant

TGV = Thoracic gas volume

TLC = Total lung capacity

TLCO = Transfer factor of the lung for carbon monoxide

TV = Tidal volume

UAO = Upper airway obstruction

UK = United Kingdom

UPDRS = Unified Parkinson's Disease Rating Scale

VA = Alveolar volume

VC = Vital capacity

VO2max = Maximal oxygen consumption

VO2peak = Peak oxygen consumption

VTA = Ventral tegmental area

6MWD = Six minute walk distance

6MWT = Six minute walk test

Chapter 1. Overview

1.1 Background and rationale to study

Pulmonary complications associated with idiopathic Parkinson's disease (IPD) are a common reason for hospital admission (Woodford and Walker, 2005, Tan et al., 1998). Lee et al 2007, evaluated symptom burden experienced by patients with IPD with 35.8% reporting shortness of breath on exertion, 17.9% reporting cough and 13% reporting sputum production (Lee et al., 2007). A higher proportion of patients with IPD die from pneumonia than in the general population (Pennington et al., 2010). Previous research into the effect of PD on pulmonary function has produced varied and conflicting results. Obstructive and restrictive ventilatory defect patterns and upper-airway and intercostal muscle problems have all been reported.

A recent review of exercise and parkinsonism underlined the improvements pertaining to both the functional deficits and neurological biomarker manifestations of the disorder and concluded that physical exercise co-administered with antiparkinsonian medication ought to contribute to an enrichment of aspects of functioning and the quality of life of PD patients (Archer et al., 2011). The review however mentioned little evidence of the effect of exercise on pulmonary function, aerobic capacity, respiratory muscle strength and breathlessness and literature review has found this area to be lacking in high quality studies. The potential benefits of an exercise intervention on factors that relate to poor quality of life in Parkinson's disease should not be underestimated. Literature review has indicated the negative impact of PD on quality of life, with many contributing factors: bradykinesia, tremor, rigidity, gait disturbance, postural instability, pain, fatigue, depression, cognitive alterations, sleep disturbances, drooling, limitations to social functioning and economic implications (Chrischilles et al., 2002, Whetten-Goldstein et al., 1997, Schrag et al., 2000, Leibner et al., 2010, Karlsen et al., 1999, Schenkman et al., 2001, Morimoto et al., 2003).

Thus further research looking at pulmonary function, respiratory muscle strength, aerobic capacity, and exercise capacity in different stages of the disease, and the response to an exercise intervention in IPD, was indicated. With the significant impact of IPD symptoms on quality of life there was further

justification in assessing this secondary outcome measure of an exercise intervention also. A cross-sectional study of pulmonary function and respiratory muscle strength in IPD was undertaken. Additionally a randomised control trial (RCT) to research the effect of structured exercise therapy on cardiorespiratory fitness (aerobic capacity), exercise capacity and pulmonary function was also undertaken. The background, methods, results and conclusions of the cross-sectional study and the RCT are discussed in this thesis.

1.2 Outline of study aims and hypotheses

The aims of this study were; to establish if pulmonary function is impaired in IPD and secondly to establish whether pulmonary function, cardiorespiratory fitness and exercise capacity can be improved in IPD with structured exercise therapy. These aims were achieved through the following objectives; to define the pattern of respiratory dysfunction in IPD and to establish whether a community based structured exercise therapy programme improves pulmonary function, cardiorespiratory fitness (aerobic capacity) and exercise capacity in people with IPD.

The hypotheses of this study were:

1. Pulmonary function is impaired in IPD
2. Structured exercise therapy can improve cardiorespiratory fitness in IPD
3. Structured exercise therapy can improve exercise capacity in IPD
4. Structured exercise therapy can improve pulmonary function in IPD

Chapter 2. Introduction and literature review

2.1 General introduction

This thesis details a cross-sectional study of pulmonary function and respiratory muscle strength in IPD, and a RCT to research the effect of structured exercise therapy on cardiorespiratory fitness (aerobic capacity), exercise capacity and pulmonary function in IPD. Chapter 2 is the introduction and literature review that is divided into 3 sections; Parkinson's disease, pulmonary function and cardiorespiratory fitness. The PD section focuses on; epidemiology, aetiology, pathophysiology, clinical features, diagnosis, treatment and prognosis. The pulmonary function section focuses on; quantification of pulmonary function, spirometry, flow volume loops, lung volumes, diffusion capacity, respiratory muscle function, pulmonary function and ageing, pulmonary function and neurodegenerative disease and pulmonary function and PD. The cardiorespiratory fitness section focuses on; quantification of cardiorespiratory fitness, cardiorespiratory fitness and ageing, cardiorespiratory fitness and neurodegenerative disease and cardiorespiratory fitness and PD. Chapter 3 details the methods of the cross-sectional study; the pattern of pulmonary dysfunction in IPD. Chapter 4 reports the results, discussion and conclusion of the cross-sectional study. Chapter 5 details the methods of the RCT; the effect of an exercise intervention on pulmonary function, cardiorespiratory fitness and exercise capacity in IPD. Chapter 6 reports the results, discussion and conclusion of the RCT. Finally, prior to the references and appendices, chapter 7 is the overall conclusions and suggestions for further studies.

2.2 Parkinson's disease

Parkinson's disease (PD) is a complex, progressive, neurodegenerative disorder, secondary to dopaminergic depletion, which primarily affects motor control via the basal ganglia. PD has both motor and non-motor symptoms due to a spreading process of neuronal loss (Dexter and Jenner, 2013). It is a multi-system disease affecting dopaminergic neurones throughout the body. To date only symptomatic treatment exists, the degenerative process cannot be arrested and the cause remains elusive (Dexter and Jenner, 2013). Although the UK Brain Bank Criteria for PD diagnosis focuses mainly on motor symptoms, it is accepted that non-motor symptoms also contribute to the significant symptom burden experienced by patients with PD. The myriad of

potential non-motor symptoms associated with PD has led to increasing research in this area in attempts to improve quality of life in those affected.

2.2.1 Epidemiology

The median age of onset of PD is 60 years and the incidence of PD rises with age up to the start of the ninth decade after which there is a decrease (Lees et al., 2009, Taylor et al., 2005). A wealth of data exists supporting that men are more likely to develop PD than women, however a systematic review of twenty five incidence studies highlighted that this difference may be restricted to western populations and is more pronounced in those over 70 years of age, with only five of the reviewed studies reporting a significantly higher incidence in men (Twelves et al., 2003).

The reported prevalence of PD varies throughout the world. This variance is likely multifactorial due to populations and ages studied, methodological and diagnostic criteria differences. In the United Kingdom (UK) PD is the second most common neurodegenerative disorder after Alzheimer's disease (Archibald and Burn, 2008). Local incidence and prevalence studies in the North east of England found the crude incidence of PD in more urban areas (Newcastle and Gateshead) to be 15.9 per 100 000 persons per year or 12.0 per 100 000 when age standardised to European studies and in a more rural population crude and age-adjusted prevalence estimates of 148 cases and 139 cases per 100,000 respectively (Duncan et al., 2014, Porter et al., 2006). A systematic review of 39 European incidence and prevalence studies found 87% reported estimates of prevalence rates, while only 13% reported incidence rates with crude prevalence rate estimates ranging from 65.6 per 100,000 to 12,500 per 100,000 and incidence estimates from 5 per 100,000 to 346 per 100,000 (von Campenhausen et al., 2005). Despite prevalence rate calculations being crude, PD appears less common in Asian countries (Chen and Tsai, 2010). In 2009, using the world's largest anonymised longitudinal computerised database of medical records, UK PD prevalence rates were found to be 30.9/10,000 for males and 24.1/10,000 for females translating to 69,850 males and 57,043 females with the condition (Parkinson's UK, 2009). A 2017 Parkinson's UK publication updated UK incidence and prevalence figures using data taken from the May 2016 static version of the Clinical Practice Research Datalink (CPRD) using the primary care database (GOLD). The data included patients aged 20 or

over with a record for Parkinson's in their file from the 1st January 1988 to the 31st December 2015. Prevalence rates refer to that in 2015, incidence rates use combined data over a 5 year period (2011-2015) to give more reliable estimates. The data revealed that in the UK in 2015 approximately 2 in 1000 people live with PD. This can be broken down more specifically into 18 in every 10000 females and 25 in every 10000 males. Focussing on the adult population alone this is approximately 3 in every 1000 people (22 in every 10000 women and 32 in every 10000) men. This data indicates that in 2015 there were around 137000 people in the UK with PD (57.7% male). Incidence figures concluded that around 3 in every 10000 women and 4 in every 10000 men will have a new diagnosis of PD each year with incidence numbers suggesting around 17300 new diagnoses of PD in the UK each year (Parkinson'sUK, 2017).

Thus between the 2009 and 2017 Parkinson's UK publications the prevalence of PD in the UK has risen by over 10000. The most likely reason for this increase and the increase in incidence is that the UK population is increasingly ageing with increasing life expectancy, and with the median age of onset of PD being 60 years PD is more common in this older expanding age group. Improvements in the way PD is diagnosed both with improved clinical knowledge and the introduction of improved tests, for example DaTSCAN^{TM}, this has likely contributed to higher diagnosis rates and thus increased prevalence and incidence. With projected increases in the elderly population and increasing research into knowledge and diagnostic testing, the prevalence and incidence of PD is set to increase.

2.2.2 Aetiology

Although biblical texts vaguely describe cases that may be consistent with what we now identify as PD, no clear, succinct case series describing clinical features was published until the 1817 "An Essay on the Shaking Palsy" by Hoxton surgeon and apothecary, James Parkinson (Stern, 1989, Parkinson, 2002). Subsequent neurologists advanced our knowledge of the disease, most notably the eminent Jean-Martin Charcot who advocated the label "maladie de Parkinson" or Parkinson's disease in place of "Paralysis Agitans" or the "Shaking Palsy" (Lees, 2007). Despite advances, the large time scale and extensive research, the cause of PD remains elusive. As highlighted, age is a

major risk factor however the cause of PD is likely a complex interaction between genetic and environmental factors.

Considered a sporadic disease, the cause of PD in 95% of cases remains unknown and is so called idiopathic Parkinson's disease (IPD). Only as recently as the last two decades have susceptibility factors and causative factors been identified in familial PD in the remaining 5% (Schapira, 2006, Lesage and Brice, 2009). Increasing research evidence supports conclusions that PD development is contributed to by abnormal handling of misfolded proteins by the ubiquitin-proteasome and autophagy-lysosomal systems, increased oxidative stress, mitochondrial and lysosomal dysfunctions (Lesage and Brice, 2009). After age, family history remains the second largest risk factor for developing PD with those with PD being four times more likely to have an affected first degree relative (Payami et al., 1994).

Genetic studies have identified a number of genetic mutations associated with autosomal dominant and autosomal recessive familial PD. Mutations inherited in an autosomal dominant manner include those in the α-Synuclein (SNCA) and leucine rich repeat kinase 2 (LRRK2) genes (Polymeropoulos et al., 1997, Zimprich et al., 2004). Those inherited in an autosomal recessive manner include mutations in Parkin, PTEN-induced putative kinase 1 (PINK1), DJ-1 and ATP13A2 (Kitada et al., 1998, Valente et al., 2004a, Valente et al., 2004b, Bonifati et al., 2003, Ramirez et al., 2006). Mutations in LRRK 2 are the most common, particularly in north African Arabs, Ashkenazi Jews and in the Portuguese, with Parkin mutations being the second commonest genetic cause (Healy et al., 2008, Lees et al., 2009). Genetic mutations are more common in those with young onset parkinsonism however their clinical presentation, associated features and pathology vary between mutations. Mutations in LRRK 2 resemble sporadic PD but tend to follow a more benign course with reduced incidence of dementia (Lees et al., 2009). Unfortunately current PD genetics nomenclature is a constant source of confusion and misinterpretation with an incomplete list of genes, and inconsistencies with confirmed, non-confirmed and duplicated loci (Marras et al., 2012, Klein and Westenberger, 2012).

A selection of environmental factors have been implicated in the aetiology of PD. Dating back over 30 years, prospective and retrospective studies have demonstrated an inverse correlation between PD and smoking concluding there is a reduced risk of developing PD in smokers (Checkoway et al., 2002, Marttila

and Rinne, 1980, Baumann et al., 1980). A more recent study including 305,468 participants, of whom 1,662 had PD, found compared with never smokers, the multivariate odds ratios (OR) were 0.78 for past smokers and 0.56 for current smokers and on close inspection of the data found that smoking duration was more associated with lower PD risk than smoking intensity (Chen et al., 2010). Epidemiological, clinical and animal studies also support the antiparkinsonian potential of caffeine, an adenosine A2A receptor antagonist, with data to suggest that caffeine may confer protection against dopaminergic neuron degeneration and delay disease onset and progression (Prediger, 2010). Istradefylline, a caffeine analog and adenosine A2A receptor antagonist, has recently received approval for use in limited countries (Dungo and Deeks, 2013). With dopamine's links to pleasure seeking behaviour, some debate remains as to whether the reduced caffeine and smoking in the premorbid state are epiphenomena rather than causally related and reflect premorbid attitude and low sensation seeking character traits (Evans et al., 2006, Jimenez-Jimenez et al., 1992).

In 1976 a Maryland scientist made an error whilst trying to manufacture Desmethylprodine 1,3-Dimethyl-4-phenyl-4-propionoxypiperidine (MPPP), an illegal synthetic opioid, and instead created 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) having injected this he rapidly developed symptoms of PD within days, a similar effect was noted in a group of heroin users in 1982 who injected MPTP contaminated heroin (Langston, 1996, Langston et al., 1983). Pathological data showed MPTP was selectively neurotoxic to dopaminergic neurons in the substantia nigra (Langston et al., 1983). The discovery of the neurotoxic effect of MPTP created a research rejuvenation in PD particularly focused on potential environmental neurotoxins. Research supports, in varying strengths, the associations between pesticide exposure, rural living, farming, well-water drinking and the development of PD, however further research is warranted in this area as stronger associations were noted in those with genetic susceptibility (Priyadarshi et al., 2001, Gorell et al., 1998, Semchuk et al., 1992, Freire and Koifman, 2012).

2.2.3 Pathophysiology

Movement occurs in response to signals from the corticospinal and reticulospinal tracts, with the corticospinal being of most importance. The

corticospinal tract, whilst having contributions from some pre-motor areas, originates predominantly from the primary motor cortex. The primary motor cortex receives input from cortical and subcortical structures. The basal ganglia is one of the major subcortical systems that receives input from the cortex and sends processed information via the thalamus back to the cortex and mainly influences the magnitude of, and which, movements to make (Wolters and Baumann, 2014).

The basal ganglia is composed of four main nuclei; striatum, pallidum, subthalamic nucleus and substantia nigra. The striatum is comprised of the caudate nucleus, putamen and nucleus accumbens. The pallidum is comprised of the ventral pallidum and internal and external globus pallidus. The substantia nigra consists of the pars compacta, which contains the dopaminergic neurons, and the pars reticulata. The basal ganglia receive inputs from almost all parts of the cerebral cortex with the striatum being the main input structure. Dopamine fibres stemming from the substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA), medial to the substantia nigra, modulate information transfer at striatum level (Wolters and Baumann, 2014). Whilst the majority of projections terminate in the striatum and pallidum, other projections extend to the cortex, thalamus and alternative brainstem areas (Archibald and Burn, 2008). Deficiency of dopamine is the characteristic hallmark of PD, from profound dopaminergic cell loss in the SNc causing degeneration of these projections (Archibald and Burn, 2008). The effect of this dopamine loss is malfunction of the extremely complex direct and indirect pathways, excitatory and inhibitory circuits.

Accompanying this selective loss of dopaminergic neurons, pathological confirmation of diagnosis focuses on the finding of Lewy bodies (LBs) and Lewy neurites (LNs) (Dickson et al., 2009). LBs are cytoplasmic inclusions whilst LNs are abnormal neuritic depositions (Dijkstra et al., 2014). The major component of LBs and LNs is a protein called α-synuclein (Spillantini et al., 1997). α-synuclein is normally highly abundant in the brain and other tissues, however the exact physiological function of this protein is not yet fully understood but is considered to have a role in neurotransmitter release including dopamine (Marques and Outeiro, 2012). In LBs and LNs, α-synuclein forms abnormal aggregations leading to cellular dysfunction. Although research continues into the actual pathological role of LBs and LNs, the most probable conclusion is

that they lead to cell death (Cookson, 2009). Whilst α-synuclein is the main component of these inclusions, over 70 other components have also been identified including; synphilin-1-binding proteins and components of the ubiquitin-proteasome system (Wakabayashi et al., 2007, Beyer et al., 2009). As discussed the aetiology in 95% of cases of PD is unknown, with identified genetic mutations, including mutations in the α-synuclein gene, in the remaining 5%. In this remaining 95% evidence suggests a role for inflammation, oxidative stress, environmental toxins, excitotoxicity and loss of neurotrophic support in promoting this abnormal protein misfolding within the brains of individuals affected by PD (Brundin et al., 2008).

The pathological processes occurring in PD begin years, even decades, before the appearance of the classical motor features and presentation of the affected individual to medical services. This period is often termed the premotor phase. Research over the last two decades has confirmed that the pathological lesions associated with PD are far more widespread and extensive than just involving the SNc. Heiko Braak and colleagues described a theory of pathological progression involving six stages marked by the continued development of LBs and LNs. Stages I and II incorporate pathology in the olfactory regions and lower brain stem (dorsal motor nucleus of the vagus nerve, intermediate reticular zone, coeruleus-subcoeruleus complex). In stages III and IV aggregations progress to basal portions of the midbrain and forebrain (notably the SNc), and the temporal mesocortex including the transentorhinal region and also involving the hippocampus. In stages V and VI, we see the final stages and the greatest topographic disease extent, with the temporal mesocortex as a beginning point lesions progress to involve the entire neocortex (Braak et al., 2004). The progression of LB and LN pathology has been correlated with the appearance and progression of motor and non-motor symptoms of PD (Halliday and McCann, 2010). Initially termed the presymptomatic phase, when pathology would be restricted to Braak stages I-III, non-motor symptoms may be apparent, for example anosmia, and thus this is better termed the premotor phase (Braak et al., 2004, Halliday and McCann, 2010). Braak stages IV-VI herald the more recognisable motor symptoms, with later stages showing cognitive disturbances (Halliday and McCann, 2010, Halliday et al., 2011).

Although there is widespread support for the Braak hypothesis, questions remain around the lack of correlation between the staging and clinical severity

highlighted by many asymptomatic elderly with widespread α-synuclein deposition (Burke et al., 2008). Importantly not all familial cases of PD have LB pathology but all have SNc degeneration (Santpere and Ferrer, 2009). The propagation of cellular pathology in PD continues to receive considerable research interest. Post mortem studies of individuals with advanced PD who received fetal nigral mesencephalic cell transplantation demonstrated Lewy pathology within the grafted neurons and laboratory and animal studies have confirmed that α-synuclein can transfer from affected to unaffected nerve cells which supports the hypothesis that α-synuclein is a prion-like protein and PD thus a prion-like disorder (Olanow and Brundin, 2013). Acknowledged by Braak and colleagues, Lewy pathology is not restricted to the brain, with involvement of the enteric nervous system and early positive biopsies of the gastrointestinal system (Braak et al., 2003, Hawkes et al., 2007, Lebouvier et al., 2010). Lewy pathology has also been found to affect the autonomic nervous system, including the cardiovascular autonomic system, with research in this area importantly continuing to answer currently elusive questions surrounding why not all individuals with PD suffer autonomic dysfunction and why presence of pathology does not always translate into symptoms (Ferrer, 2011). As well as the widely known dopaminergic depletion, PD is also associated with impaired noradrenergic, cholinergic and serotoninergic innervation (Ferrer, 2011). Once considered a motor disorder, PD is increasingly recognised as a complex multi system disease and the complexity and scale of the identified pathology correlates with the vast array of potential signs and symptoms of the disease. The identification of potentially quantifiable or accessible markers of PD, including neurotransmitters and biopsy targets, remains of high importance particularly in potentially identifying those in the so called premotor or presymptomatic phase of the disease if neuroprotective therapy is developed.

2.2.4 Clinical features

There is considerable heterogeneity in the clinical phenotype of PD and the multisystem disease pathology leads to a wide range of possible signs and symptoms (Foltynie et al., 2002). PD is characterised by a multifaceted picture of motor and non-motor symptoms that is not only different between patients but along the course of disease in individual patients (Moustafa and Poletti, 2013).

The four cardinal clinical features and motor symptoms of PD are; bradykinesia, tremor at rest, rigidity and postural instability, with bradykinesia being the key clinical feature in order to make a diagnosis. Bradykinesia strictly means slowness of a performed movement however the term is often used interchangeably with akinesia or hypokinesia (Berardelli et al., 2001). Akinesia refers to paucity of a spontaneous movement or associated movement, for example facial movement or arm swing with gait respectively; and hypokinesia means movements are small in addition to being slow (Berardelli et al., 2001). The classical tremor associated with PD is a tremor of 4-6 Hz at rest that begins unilaterally. Hand tremors are often described as “pill rolling” and tremor can be evident in the legs, lips, chin and jaw with postural re-emergent tremor also a feature. (Jankovic, 2008). The classical tremor characteristically disappears or improves with action or on sleeping (Jankovic, 2008). Rigidity in PD refers to increased resistance when passively stretching a muscle (Berardelli et al., 1983). This rigidity is frequently described as “lead pipe rigidity” describing rigidity present throughout the full range of movement. A cogwheel sensation represents tremor superimposed on rigidity. Rigidity may be felt in the limbs or more proximally, termed axial rigidity, in the neck and trunk. Postural instability is a particularly disabling feature with many contributory factors, in addition to loss of postural reflexes, contributing to balance impairment and falls (Bloem, 1992).

Freezing, considered an akinesia, is a debilitating motor symptom that predominantly affects gait but can affect other actions including speech. Although more common in the “off” state, it can also occur in the “on” state and affected individuals describe a sudden feeling that their feet are glued to the floor and they are unable to move them. Freezing is a transient phenomenon during which individuals may have to implement sensory tricks or cues to continue the intended movement (Nieuwboer, 2008). Widely acknowledged and frequently termed secondary motor symptoms seen in PD include; hypomimia, bulbar dysfunction (manifested as dysarthria, dysphagia, sialorrhea and hypophonia), gait disturbances (shuffling, festination), reduced arm swing, difficulty standing from a sitting position, difficulty turning in bed, micrographia, slow activities of daily living, glabellar reflex, dystonia, neuro-ophthalmological problems (reduced blink rate, eyelid opening apraxia and blepharospasm which is considered focal dystonia), striatal deformity, scoliosis and camptocormia

(Jankovic, 2008). Camptocormia, caused by axial dystonia in PD, is an abnormal flexion of the trunk that appears in the standing position, worsens on walking and abates when supine (Lenoir et al., 2010). Originally thought to be a rare symptom, a recent single centre study of 275 patients reported prevalence rates of Camptocormia of 6.9% (Tiple et al., 2009).

The importance of the identification of non-motor symptoms in PD is becoming increasingly recognised. Non-motor symptoms are sometimes present pre-diagnosis, almost always occur with advancing disease and significantly contribute to impaired quality of life, morbidity and mortality (Chaudhuri et al., 2006, Chaudhuri and Schapira, 2009). Non-motor symptoms are under recognised and under reported resulting in under treatment, with up to 62% of non-motor symptoms remaining undeclared due to embarrassment or lack of knowledge of their association with PD (Chaudhuri et al., 2010). Potential individual non-motor symptoms are so numerous that they are best considered in groups; neuropsychiatric, sleep disorders, autonomic symptoms, gastrointestinal symptoms and sensory symptoms.

Neuropsychiatric symptoms are wide ranging from depression, apathy, anxiety, anhedonia, fatigue, repetitive behaviour, delirium, hallucinations, delusions and dementia (Chaudhuri et al., 2006). Depression is more prevalent in PD than in the general population and also a diagnosis is more common in PD patients before the onset or diagnosis of their PD (Ishihara and Brayne, 2006). The prevalence of dementia in PD is high and is associated with a more rapid decline (Aarsland et al., 2003, Aarsland et al., 2004). Some of the myriad of potential neuropsychiatric symptoms, including delirium, obsessional behaviours and impulse control disorders may also be a consequence of drug treatment for other PD symptoms.

Rapid eye movement (REM) sleep behaviour disorder (RBD) is seen in association with PD and remains an important potential preclinical marker for researchers with 40% of individuals with a diagnosis of idiopathic RBD developing an alpha-synuclein pathology after an average of five years follow up (Britton and Chaudhuri, 2009). Nocturnal sleep disturbances also include insomnia, nightmares, restless legs, vivid dreaming and sleep disordered breathing and day time symptoms of excessive sleepiness are common (Chaudhuri et al., 2006, Kumar et al., 2002, Chotinaiwattarakul et al., 2011).

Urinary symptoms associated with autonomic disturbance, are the most commonly reported non-motor symptom in PD (Martinez-Martin et al., 2007). Urinary symptoms include urgency, nocturia and frequency, with additional autonomic symptoms of sweating, orthostatic hypotension, sexual dysfunction and dry eyes (Chaudhuri et al., 2006). Symptoms of orthostatic hypotension also increase risk of falls and subsequent injury and loss of confidence. Gastrointestinal non-motor symptoms; nausea, constipation, reflux, incontinence, share commonality with autonomic symptoms as part of the disease complex (Chaudhuri et al., 2006).

Sensory symptoms, particularly pain, are frequently not recognised as part of the PD complex and can be difficult to quantify and categorise. Pain, of varying characteristics, is a frequent sensory symptom observed in PD (Beiske et al., 2009). Musculoskeletal, dystonic, neuropathic and central pains have all been reported with musculoskeletal pain present in up to 70% (Beiske et al., 2009). Like RBD, olfactory dysfunction with hyposmia is a common finding in PD and a diagnosis of idiopathic olfactory dysfunction is associated with an increased risk of developing PD and thus may also prove to be an important pre-clinical marker when researching neuroprotective agents (Ponsen et al., 2004).

By the time motor symptoms are recognised the pathological process in PD is advanced. The duration of this pre-motor phase, during which neurodegeneration is occurring, remains contentious with estimations ranging from 3.1 to 20 years (Hoehn and Yahr, 1967, Fearnley and Lees, 1991, Vingerhoets et al., 1994, Morrish et al., 1996). It is accepted that motor symptoms occur when dopaminergic cell loss in the SNc reaches a critical level and this is most frequently quoted to be 50-60% loss. Non-motor symptoms predominate in this pre-motor phase and identification of these could provide the key for neuroprotection. In addition to RBD and hyposmia, there is strong evidence for constipation and depression as pre-motor characteristics and increasing evidence that urinary and sexual dysfunction and chronotropic insufficiency may also serve as potential pre-motor PD biomarkers (Chaudhuri et al., 2006, Palma et al., 2013, Palma and Kaufmann, 2014). Weaker evidence exists for the suggested links of restless-legs syndrome, apathy, fatigue and anxiety to the pre-motor phase (Chaudhuri et al., 2006).

The symptom burden experienced by individuals with PD is easily apparent and with the absence of curative treatment, reduction of symptom load remains the

aim. The most common tool for assessing symptom load in PD is the Unified Parkinson's Disease Rating Scale (UPDRS) however this is more focussed on motor rather than non-motor symptoms. Prior to 2006 there was no single instrument for comprehensive assessment of non-motor symptoms thus the Non Motor Symptoms Screening Questionnaire (NMSQuest) was developed and validated (Martinez-Martin et al., 2007). An observational, multicentre, international cross-sectional study of 545 PD patients used the NMSQuest to quantify the prevalence of non-motor symptoms and reported urinary symptoms to be the most prevalent, in particular nocturia reported in 61.9% (Martinez-Martin et al., 2007). The NMSQuest has 9 domains with a number of questions in each domain. In the afore mentioned study the percentage of individuals scoring the maximum for each domain was reported as; urinary 59%, depression/anxiety 48%, apathy/attention/memory 42%, sleep disorder 37%, sexual function 33%, cardiovascular 32%, digestive 29%, miscellaneous 25%, hallucinations/delusions 17% and importantly only 1.6% (8 individuals) reported no non-motor symptoms at all (Martinez-Martin et al., 2007).

While no unequivocally neuroprotective or neurorestorative treatments for PD exist, the management remains that of symptom control. Symptom control is one of the central goals of palliative medicine and assessment tools from this specialty can provide important information to help manage PD patients. Despite the introduction of the NMSQuest and the use of the UPDRS, not all potential PD associated symptoms are identified with these tools. A descriptive cross-sectional survey using a standard palliative care assessment tool highlighted the frequency of other symptoms in a representative population with IPD (n=123) including shortness of breath on exertion (35.8%), cough (17.9%) and sputum (13%) (Lee et al., 2007). The use of this alternative tool reported concerning percentages reporting respiratory symptoms, a domain not covered in alternative assessments.

Categorising patients can be very useful particularly when considering treatment and prognosis. With the myriad of potential symptoms in IPD, categorising individuals on clinical (motor) phenotype, based on signs and symptoms, into tremor dominant (TD) or postural instability gait difficulty (PIGD) subtypes is a recognised technique. Formulas have been developed to categorise TD and PIGD phenotypes from the UPDRS making this widely used (Stebbins et al., 2013). Large studies provide support for these clinical

phenotypes that have in addition been reported to have differences on molecular imaging and basal ganglia output (Jankovic et al., 1990, Zaidel et al., 2009, Schillaci et al., 2011).

Whilst formulas have been developed, research continues to identify clinical features associated with different phenotypes that may have prognostic and treatment implications. Prior to interpretation of extrapolated data from the Tracking Parkinson's study, no large scale studies (n > 400) had specifically focused on the association of vascular risk factors and vascular disease with motor features and cognition in early PD. Cardiovascular disease describes a group of diseases of the heart and blood vessels for example; angina, myocardial infarction, stroke, transient ischaemic attack and peripheral arterial disease. Vascular risk factors are characteristics or exposures that increase the likelihood of developing vascular disease or diseases. Vascular risk factors are numerous and include for example; smoking, hypertension, hypercholesterolaemia, obesity and diabetes. Common cerebrovascular pathologies, including macroscopic infarcts, microinfarcts, and arteriolosclerosis, often seen in older persons, can cause mild parkinsonian signs, particularly parkinsonian gait (Buchman et al., 2011). This is often termed vascular parkinsonism. Malek et al reported,from 1759 PD cases, patients with cerebrovascular disease, in the manner of previous stroke or transient ischaemic attack, were more likely to have PIGD phenotype and cognitive impairment, this however failed to reach statistical significance after age, sex and disease duration adjustments. They also reported more than 2 vascular risk factors were associated with worse UPDRS 3 motor scores and cognitive impairment. In those who had had structural brain imaging, the presence of white matter change was associated with PIGD and cognitive impairment. The latter two associations reached statistical significance (Malek et al., 2016).

Differentiating between the TD and PIGD phenotypes, and identifying risk factors for these phenotypes, is important both clinically and in research settings as they have been correlated to different associated features, progression and prognosis.

2.2.5 Diagnosis

Parkinson's disease is a clinical diagnosis which can only be pathologically confirmed by the findings of LB pathology on post mortem. Advances in structural and functional neuroimaging have provided support in the diagnosis of PD and differential diagnosis of other parkinsonian disorders. To make a diagnosis of PD requires the essential finding of bradykinesia with at least one of: rest tremor, rigidity or postural instability. The UK Brain Bank developed criteria to aid diagnosis, which are illustrated in Table 1.

UK Brain Bank clinical diagnostic criteria

Step 1. Diagnosis of Parkinsonian Syndrome

Bradykinesia

At least one of the following:

- Muscular rigidity
- 4-6 Hz rest tremor
- Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Step 2. Exclusion criteria for Parkinson's disease

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Definite encephalitis or oculogyric crisis on no drug treatment
- Neuroleptic treatment at onset of symptoms
- More than one affected relative
- Sustained remission
- Strictly unilateral features after 3 years
- Other neurological features: early severe autonomic involvement, Babinski sign, cerebellar signs, supranuclear gaze palsy, early severe dementia with disturbances of memory, language, and praxis
- Presence of cerebral tumour or communicating hydrocephalus on imaging
- Negative response to large doses of levodopa in absence of

malabsorption • Exposure to known neurotoxin
Step 3. Supportive prospective positive criteria for Parkinson's disease Three or more required for diagnosis in combination with step one: • Unilateral onset • Rest tremor present • Progressive disorder • Persistent asymmetry affecting side of onset most • Excellent response (70-100%) to levodopa • Severe levodopa-induced chorea (dyskinesia) • Levodopa response for 5 years or more • Clinical course of ten years or more

Table 1: UK Brain Bank Parkinson's disease diagnostic criteria

Clinicopathological studies have reported significant false-positive and false-negative rates for diagnosing parkinsonian disorders, particularly in the early stages of disease (Litvan et al., 2003). Misdiagnosis can arise for numerous reasons and it is imperative to remember that parkinsonism describes the clinical features seen in PD and does not necessarily imply the diagnosis is IPD, and that tremor is not needed to diagnose PD and the presence of tremor does not necessarily imply IPD (Archibald and Burn, 2008).

Parkinson's disease may be considered to be either idiopathic PD (IPD), sometimes termed sporadic accounting for 95% of cases, or genetic PD accounting for only 5% of cases. There are multiple differential diagnoses to consider when assessing an individual with parkinsonism or tremor, and comprehensive history taking can provide vital clues. The clinical features of parkinsonism can be secondary, caused by another event or substance, and include vascular parkinsonism and drug induced parkinsonism. Vascular parkinsonism, caused by ischaemic cerebrovascular insults, accounts for 2.5-5% of cases of parkinsonism and usually presents with a step-wise deterioration predominantly affecting the lower limbs (Gupta and Kuruvilla, 2011). Drug induced parkinsonism is frequently symmetrical and temporally associated with causative drug use (Archibald and Burn, 2008). Initially reported as a complication of neuroleptics, it has subsequently been described with a diversity

of drugs including antiemetics, anti- vertigo drugs, antidepressants, calcium channel antagonists, antiarrhythmics, antiepileptics and others. Whilst traditionally considered reversible after drug withdrawal it persists in excess of 10% of people which may indicate drug-unmasked PD (Mena and de Yebenes, 2006).

Parkinson-plus syndromes, also known as atypical parkinsonian disorders or disorders of multiple system degeneration, display the classical features of a parkinsonian disorder but with extra features that differentiate them from IPD. The Parkinson-plus syndromes include; multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and dementia with Lewy bodies (DLB). Accompanying the parkinsonism and amongst other symptoms, MSA is associated with cerebellar features and early autonomic features, PSP with early backward falls and supranuclear opthalmoplegia, CBD with apraxia, alien limb phenomena and aphasia, and DLB with hallucinations and early cognitive decline (Poewe and Wenning, 2002). Further differential diagnoses that need to be considered include functional or non-organic disorders, normal pressure hydrocephalus and Wilson's disease (Archibald and Burn, 2008). In the presence of tremor, essential tremor, cerebellar disorders, physiological causes of tremor (e.g. thyrotoxicosis) and dystonic tremor need to be excluded (Bhidayasiri, 2005).

Advances in functional imaging techniques over recent years have assisted in improving diagnostic accuracy and thus guiding appropriate management. Conventional structural imaging techniques, for example magnetic resonance imaging (MRI), are useful in the investigation of suspected vascular parkinsonism or for the exclusion of space occupying lesions. By labelling the dopamine transporters in the basal ganglia with radioisotopes, Ioflupane (^{123}I) (DaTSCAN^{TM}), single-photon emission computed tomography (SPECT) images can be obtained to assess the integrity of the dopaminergic system. Normal images suggest a diagnosis not involving nigrostriatal neurodegeneration, for example essential tremor, vascular parkinsonism or drug induced parkinsonism (Cummings et al., 2011). Abnormal imaging indicates underlying nigrostriatal neurodegeneration thus supports a diagnosis of PD or a Parkinson-plus syndrome but cannot differentiate between these (Cummings et al., 2011). Further imaging techniques, not necessarily brain imaging, can be useful in attempting to distinguish between PD and a Parkinson-plus syndrome. These

include autonomic testing and myocardial MIBG scintigraphy which measures the postganglionic sympathetic cardiac innervation, which can be a helpful test to differentiate PD from MSA. Despite imaging test advances, these remain imperfect and whilst very useful the diagnosis remains clinical.

2.2.6 Treatment

The management of Parkinson's disease requires a comprehensive multi-disciplinary approach. Over the course of the disease involvement can include; specialist Parkinson's clinic (usually consultant neurologist or consultant geriatrician), specialist nurses, physiotherapy, speech and language therapy, occupational therapy, dieticians and palliative care. Support groups are available to provide input for both individuals with PD and their carers, families and friends. Management focuses on treatment of motor symptoms and non-motor symptoms, complications of PD and also side effects of pharmacological therapy. It is very important to address and manage non-motor symptoms individually as although the pharmacological therapies used to treat motor symptoms can improve a selection of non-motor symptoms they can also conversely cause or exacerbate others.

No pharmacological therapy has been proven to be unequivocally neuroprotective and thus treatment remains guided by symptoms. In view of this not all patients require treatment initiation at diagnosis. NICE refer to 'early disease' as those individuals who have developed functional disability and require symptomatic therapy, and 'later disease' as those on levodopa who have developed motor complications (NICE, 2006). Whilst dopaminergic replacement therapy remains the basis of pharmacological management, guidelines to date have been unable to recommend one specific universal first line treatment in early disease or adjuvant for later disease further highlighting the need for individuals with PD to be managed by experienced teams. Pharmacological treatment options are summarised in Table 2, adapted from NICE guidance and Archibald and Burn (NICE, 2006, Archibald and Burn, 2008).

Drug class	Suitable for early treatment	Examples	Mode of action	Benefits	Disadvantages	Potential side-effects
Levodopa	Yes	Co-careldopa (Sinemet) Co-beneldopa (Madopar)	Uptake by dopaminergic neurons that remain Conversion to dopamine and released.	Well tolerated Good degree of symptom control Titration easy Different preparations available (standard, modified-release, dispersible)	Half-life 60 minutes Motor complications End-dose effect Increase risk dyskinesias Modified-release preparations should not be used to delay onset of motor complications	Nausea Vomiting Postural hypotension Confusion Somnolence Vivid dreams Hallucinations
Dopamine agonists (oral or transdermal)	Yes	Ropinirole (oral) Pramipexole (oral) Rotigotine (transdermal)	Direct stimulation of dopamine receptors	Moderate degree of symptom control Half-life varies Some available in standard and modified-release Fewer late motor complications	Elderly tolerate less well Side effects more potent	As for levodopa Impulse control disorders (ICD) Skin irritation for transdermal
Dopamine agonists (subcutaneous)	No	Apomorphine	Direct stimulation of dopamine receptors (D1 and D2)	Rapid onset Useful in severe motor complications Non oral route	Non oral Short half-life thus continuous infusion Expensive	As for levodopa Infusion site reactions
Monoamine oxidase inhibitors Type B	Yes	Rasagiline Selegiline	Inhibit MAO-B and increases available dopamine in synaptic cleft	Well tolerated Once daily	Limited symptom control compared to other agents	Headache Urinary symptoms Depression Dry mouth

						Postural hypotension
COMT inhibitors	No	Entacapone Tolcapone	Inhibit catechol-O-methyl transferase Increase half-life of levodopa	Reduce motor fluctuations	Tolcapone can cause hepatic damage thus monitoring of liver function tests required	As for levodopa Diarrhoea can be prominent and cause intolerance Urine discoloured orange Dyskinesia
Amantadine	No	Amantadine	Glutamate receptor antagonist Increases dopamine release and blocks reuptake	Help reduce dyskinesia	Limited evidence Specialist administration	Confusion Hallucinations Agitation Insomnia Ankle oedema Livedo reticularis

Table 2: Pharmacological therapy options

In advanced disease if severe motor fluctuations, arising from pulsatile dopaminergic stimulation, become unmanageable despite optimising oral or subcutaneous therapy, consideration can be given to the use of deep brain stimulation or continuous infusion of levodopa/carbidopa intestinal gel (Duodopa) via a percutaneous tube.

As illustrated in Table 2, potential side effects of dopaminergic therapy are numerous and a number are specific to anti-parkinsonian medication for example impulse control disorders. Clinicians need to remain aware of the rare iatrogenic disturbance of dopamine dysregulation syndrome, where individuals develop an addiction to dopaminergic therapy and self-administer doses in excess of those required to control motor symptoms (O'Sullivan et al., 2009). Ergot derivative dopamine agonist drugs which are no longer prescribed, including pergolide and cabergoline, are associated with valvular heart disease and lung fibrosis in addition to the other possible side effects from the drug class. Only in recent years has their prescription discontinued thus it must be remembered that many individuals with PD may have already been treated with these drugs for protracted periods.

Dopaminergic therapy must not be abruptly withdrawn as abrupt discontinuation and occasionally reduction of dose can precipitate neuroleptic malignant syndrome (Healy et al., 2008). With this is mind it is important to not allow medication to fail or a failure in administration of dopaminergic therapy. Alternative methods of administration of medication need to be considered and planned, for example in those who cannot swallow or are undergoing operations. Transdermal applications and nasogastric tubes are possible options. The complexity of PD, disease progression and antiparkinsonian medication titration, combination and potential side-effects make PD best managed by specialist services.

2.2.7 Prognosis

By definition PD is a neurodegenerative disease and while no neuroprotective agents exist, the disease process will continue to progress. Prognosis significantly varies between individuals with PD, however the commonly described clinical phenotypes of TD and PIGD are associated with differing decline rates notably in motor, non-motor and cognitive symptoms. Tremor progresses more slowly than other motor features (Vu et al., 2012).

The PIGD phenotype usually presents a more severe pattern of non-motor features, faster motor deterioration, a higher risk of developing mild cognitive impairment, faster rate of cognitive decline and is a risk factor for developing dementia (Moustafa and Poletti, 2013, Vu et al., 2012, Poletti et al., 2012, Burn et al., 2006). Depression, apathy and hallucinations are more prominent in the PIGD phenotype (Reijnders et al., 2009). PIGD appears to be less treatment responsive in those patients in the early stages of disease (Vu et al., 2012).In contrast, the TD phenotype is characterised by a less severe picture, slower motor decline, slower cognitive decline, lower dementia incidence and lower rates of depression, apathy and hallucinations (Moustafa and Poletti, 2013). Older age at onset, PIGD, dementia and depression are associated with progression of disability and a negative impact on survival (Auyeung et al., 2012, Post et al., 2007).

Individuals with PD are hospitalised in reported frequencies of up to 28% per annum, approximately 1.5 times more frequently, and generally up to 14 days longer, than non PD patients (Gerlach et al., 2011). Whilst in hospital, medication errors are frequent adverse events and after surgery PD patients have increased incidence of infection, confusion and falls (Gerlach et al., 2011). Not only does the increased hospitalisation have a negative clinical impact on the individual but also a socioeconomic one. A local study of emergency hospital admissions in IPD patients over a 4 year period, identified 246 emergency admissions accounted for by 129 patients (Woodford and Walker, 2005). The most common reasons for admission in this population were falls (13%) and pneumonia (11%) (Woodford and Walker, 2005). International retrospective studies corroborated the high frequency of these reasons to precipitate admission in PD with pneumonia or chest infection reported as the reason for admission in up to 22% and aspiration pneumonia rates more than 6 times higher than in controls (Vossius et al., 2010, Guneysel et al., 2008, Temlett and Thompson, 2006, Guttman et al., 2004, Tan et al., 1998). Other infections (including urinary tract), delirium, psychological symptoms, motor complications and PD related symptoms were also responsible for precipitating admissions.

A longitudinal, multicentre study in Australia followed PD patients, who were initially levodopa naïve at recruitment and had a mean pre-study disease duration of 23.5 months, over a 15 year period (Hely et al., 2005). One-third of

the patients had survived 15 years with non-dopaminergic problems dominating the clinical picture at that time; falls occurs in 81%, cognitive decline in 84%, dementia in 48% and choking, hallucinations and depression each in 50% (Hely et al., 2005). Hely et al, reported a significantly elevated standardised mortality ratio (SMR) at 1.86 with pneumonia being the most common cause of death in 27% with a SMR >10 (Hely et al., 2005). A local study (n=143) looked at cause of death in IPD over an 8 year period finding pneumonia as the terminal event in 45% and for those that died in hospital pneumonia was the reason for admission in 30% (Pennington et al., 2010). Previous studies corroborated high death rates from pneumonia in PD reporting rates from 20% to 27% in PD compared to 7% to 9% in control populations (Pennington et al., 2010, D'Amelio et al., 2006, Fall et al., 2003, Beyer et al., 2001). With individuals with PD demonstrating higher death rates from pneumonia, and conversely lower death rates from ischaemic heart disease, as well as higher rates of admission for chest infection and pneumonia than the general population, further research into cardiopulmonary function in IPD is indicated.

2.3 Pulmonary function

The respiratory or pulmonary system is comprised of the airways, lungs, muscles of respiration and the associated vasculature. The airways include the nose, nasal cavities, mouth, pharynx, larynx, trachea and bronchi. Within the lungs the bronchi branch into secondary then tertiary bronchi that divide into bronchioles. The bronchioles branch repeatedly into terminal bronchioles that subdivide into microscopic respiratory bronchioles and further subdivide into alveolar ducts. Surrounding these ducts are alveoli and alveolar sacs. These alveoli, the building blocks of the lungs' sponge like structure, are surrounded by a mesh of capillaries and are the site of gas exchange with the blood. The muscles involved in respiration include the diaphragm, intercostal muscles and the accessory muscles in the neck and surrounding the upper airway. Dysfunction of the respiratory system leads to increased morbidity and mortality and deterioration in quality of life. Signs and symptoms of respiratory dysfunction vary dependent on the part or parts of the pulmonary system involved. Potential signs and symptoms are numerous and may include; cough, difficulty coughing, dyspnoea, pneumonia, aspiration, reduced exercise tolerance, speech difficulties, hypophonia, atelectasis, hypoxia, hypercapnia,

sleep disordered breathing, excessive daytime somnolence, acute respiratory failure and difficulty in extubation. Iatrogenic causes of pulmonary dysfunction by medication may also be temporary or permanent.

Concomitantly with history and examination, measurement of respiratory function can be used to establish if any abnormality is present and identify particular disorders. Respiratory testing can be used to assess severity, prognosticate and serial measurements are useful to assess response to treatment or progression of disease.

2.3.1 Quantification of pulmonary function

Pulmonary function tests (PFTs) are a collection of non-invasive tests that measure airflow, lung volumes, gas exchange and respiratory muscle strength. Interpretation of tests should always begin with a review of test quality (Pellegrino et al., 2005). Quality control is important and technicians must have sufficient education and training to understand the fundamentals of the tests, signs of pulmonary disease and management of the acquired data (Miller et al., 2005a). Interpretation of PFTs is based on comparisons of measured data with reference values based on healthy subjects. Reference or predicted values should be obtained from studies of healthy subjects with the same anthropometric and ethnic characteristics as the subjects being tested (Pellegrino et al., 2005). When performing PFTs, dynamic studies (spirometry, flow volume loops, peak expiratory flow rates) are performed first followed by lung volumes and subsequently diffusion capacity (Ranu et al., 2011). Bronchodilator response and respiratory muscle strength testing may also be done in appropriate subjects.

2.3.2 Spirometry

Spirometry measures lung function by quantifying the volume and flow of air, measuring volume against time. Measurements most importantly include forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and the subsequent ratio of these values. FEV1 is the maximal volume of air exhaled in the first second of a forced expiration from a situation of maximal inspiration and is measured in litres. FVC is the maximal volume of air exhaled with maximally forced effort from a maximal inspiration, also measured in litres. FVC can also be thought of as vital capacity (VC) performed with a maximally forced expiratory effort (Miller et al., 2005b). VC is the volume change at the mouth

from full inspiration to complete expiration (Wanger et al., 2005). VC may also be referred to as relaxed or slow vital capacity (SVC). Although in normal individuals a small difference can be present in VC and FVC, this is notably exaggerated, with FVC comparatively lower than VC, in those with airflow obstruction reflecting hyperinflation and air trapping (Chhabra, 1998)

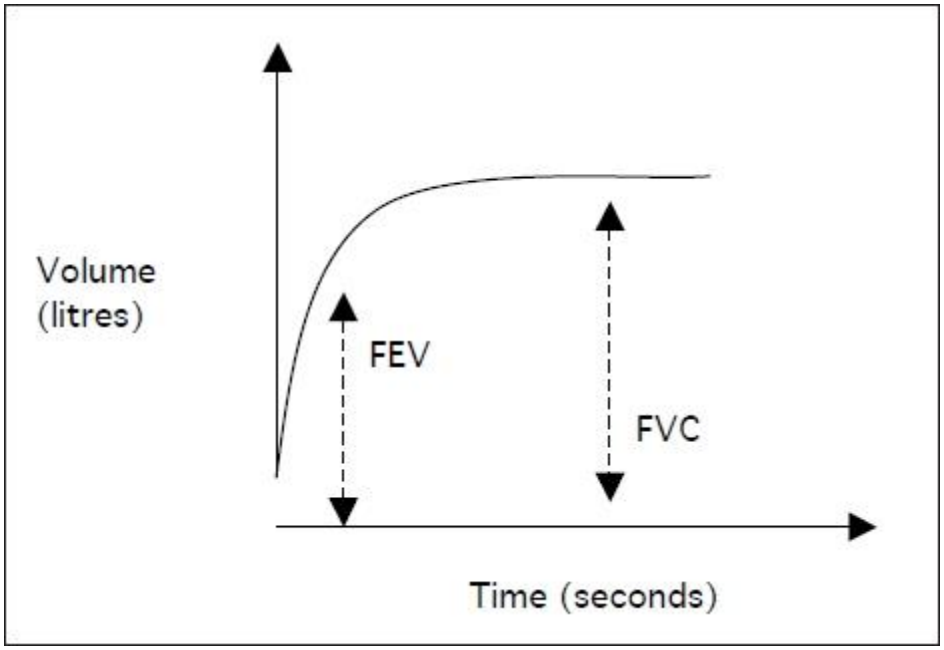

Figure 1: Normal Spirometry

(Ranu et al., 2011)

Spirometry assists in the diagnosis of ventilatory defects which, if not normal, may be obstructive, restrictive or mixed. Obstructive lung disease is characterised by lower airway obstruction and is caused by any disease that obstructs the airflow, for example by narrowing the airways. Chronic obstructive pulmonary disease (COPD), asthma and bronchiectasis are all examples of obstructive lung diseases. An obstructive ventilatory defect is represented by a disproportionate reduction in expiratory maximal airflow in relation to maximal volume, i.e. FEV1 is reduced more than FVC and thus FEV1/FVC is lowered (Ranu et al., 2011, Pellegrino et al., 2005). This reduction in the volume of air that can be forcibly exhaled in the first second suggests airway narrowing during exhalation (Pellegrino et al., 2005). Airflow obstruction is defined as a reduced FEV1/FVC ratio such that FEV1/FVC is less than 0.7 or 70% (NICE, 2010). While the British Thoracic Society (BTS) and National Institute for Health and Care Excellence (NICE) use the cut off of FEV1/FVC <0.7, the American

Thoracic Society (ATS) and European Respiratory Society (ERS) propose using a threshold below the lower limit of normal (LLN) adjusted for age (Bhatt et al., 2014). The spirometry results of the National Health and Nutrition Examination Survey (NHANES) III cohort were used to define the LLN as the fifth percentile of reference values (Hankinson et al., 1999). Debate continues into whether using the fixed ratio or LLN is superior in diagnosing obstruction, particularly in avoiding misclassification at the far ends of the age spectrum (Swanney et al., 2008, Cerveri et al., 2008, Bhatt et al., 2014). When airflow obstruction is identified with a FEV1/FVC <0.7, this can be further categorised into severity according to the reduction in FEV1. Categorised based on FEV1 %predicted; ≥80% mild or stage 1, 50-79% moderate or stage 2, 30-49% severe or stage 3, <30% very severe or stage 4 whilst noting that symptoms should be present to diagnose someone with COPD if FEV1 %predicted is ≥80% (NICE, 2010).

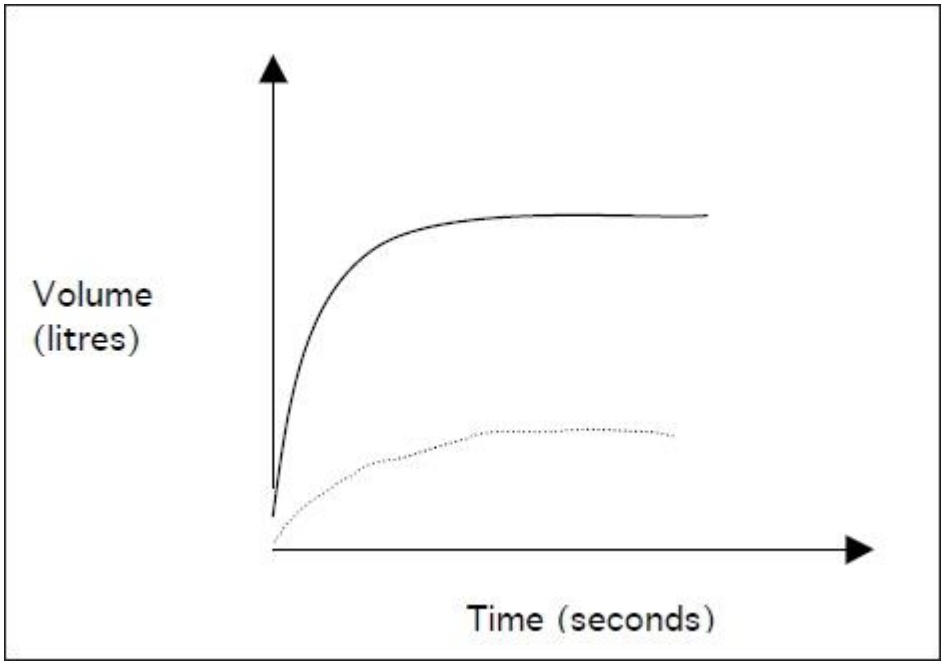

Figure 2: Obstructive spirometry

(Ranu et al., 2011)

Restrictive lung diseases are characterised by reduced lung volumes and have a variety of potential pulmonary and extrapulmonary causes. Potential pulmonary causes include interstitial lung disease, pulmonary oedema and vasculitis. Extrapulmonary causes reducing volume and expansion include neuromuscular disorders (e.g. amyotrophic lateral sclerosis (ALS), myasthenia gravis (MG), muscular dystrophies), skeletal deformities, obesity and phrenic

nerve injury. By spirometric indices a restrictive defect may be suspected if FVC is reduced <LLN or <80% predicted in the context of a normal or increased FEV1/VC or FEV1/FVC >LLN or >0.7 (Ranu et al., 2011, Johnson and Theurer, 2014, Pellegrino et al., 2005, GOLD, 2010). A restrictive pattern can only be confirmed by full lung volume testing confirming a reduction in total lung capacity (TLC) <LLN or <80% predicted (Barreiro and Perillo, 2004, Johnson and Theurer, 2014, Pellegrino et al., 2005). Although can infer a restrictive defect, FVC or VC alone have poor positive predictive value with low VC being associated with low TLC no more than fifty percent of the time (Aaron et al., 1999, Glady et al., 2003).

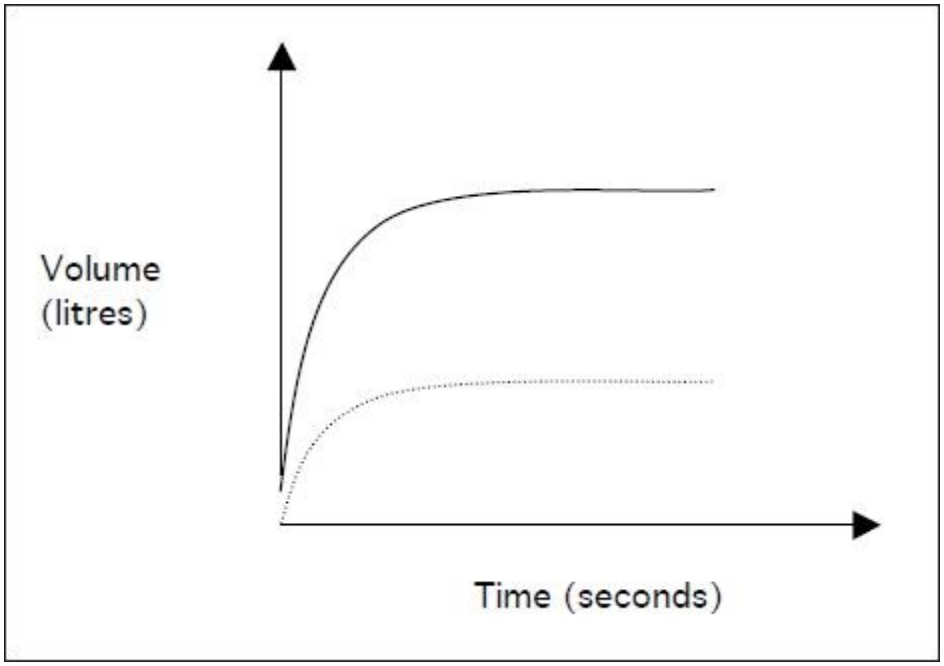

Figure 3: Restrictive Spirometry

(Ranu et al., 2011)

Mixed ventilatory defects are the co-occurrence of both obstruction and restriction with reduced FEV1/VC and reduced TLC. The measurement of TLC is necessary to accurately diagnose a mixed defect as VC or FVC can be reduced in both restriction and obstruction (Pellegrino et al., 2005).

2.3.3 Flow volume loops

Flow volume loops or curves are produced by a maximal inspiratory manoeuvre followed by a maximal expiratory manoeuvre and displayed graphically with a positive expiratory limb and a negative inspiratory limb (Ranu et al., 2011). Flow volume curves are frequently used to obtain peak expiratory flow (PEF) and the

mean forced expiratory flow between 25%-75% of FVC (FEF25-75%), the latter is also referred to as maximum mid expiratory flow (MMEF). Abnormalities in the mid-range flow measurement FEF25-75% provides information about the small airways and a reduction in this measurement can be an early change reflecting airflow obstruction in these small airways (Ranu et al., 2011, Pellegrino et al., 2005). Outwith FEV1, FVC, PEF and FEF25-75% the other numerical indices from the flow volume loop are less clinically relevant, but rather the shape of the loops, which include forced inspiratory manoeuvres, become helpful in detecting upper airway obstruction and for assessing the quality of the test (Miller et al., 2005b).

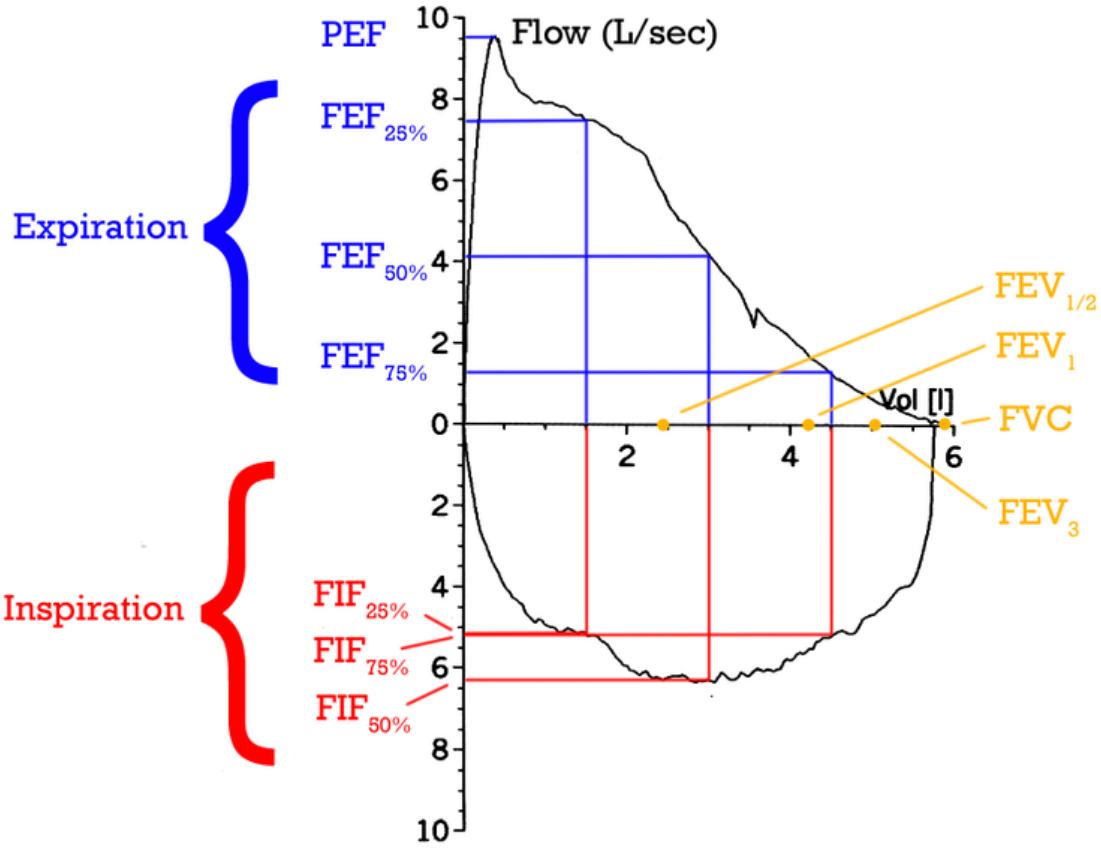

Figure 4: Labelled flow volume loop

(Wikipedia, 2004)

In obstructive lung diseases, slowing of expiratory flow is illustrated by a concave shape on the flow volume loop. Restrictive disorders produce a convex expiratory limb at reduced volumes reflecting preservation of flow rates in the context of volume loss.

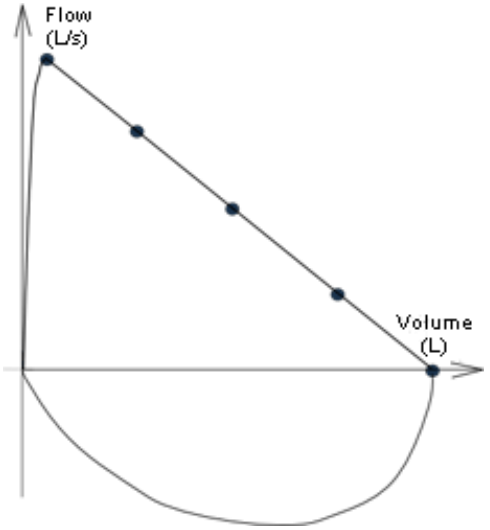

Figure 5: Normal flow volume loop

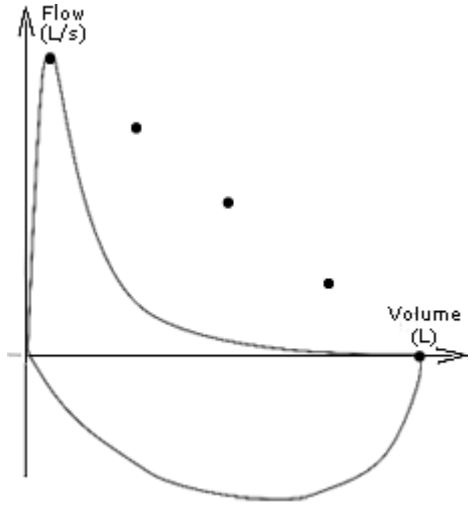

Figure 6: Obstructive flow volume loop

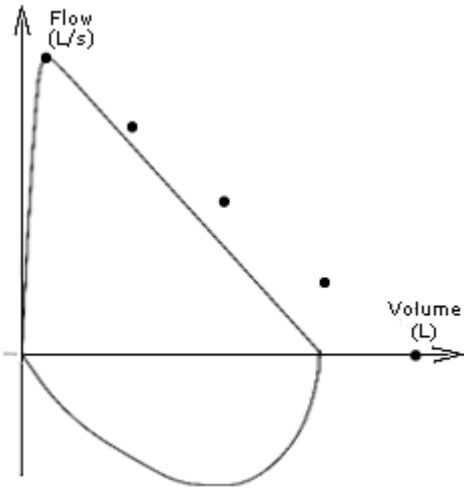

Figure 7: Restrictive flow volume loop

The shape of maximal flow volume loops can be helpful in diagnosing an upper airway obstruction (UAO) and differentiating this from lower airway. The shape can help classify the location, being extrathoracic or intrathoracic, and the nature, being fixed or variable of the obstruction. The airway can be considered in three sections, firstly the peripheral airways of 2mm diameter or less, secondly the larger or major airways from 2mm up to the carina and thirdly the upper airways including trachea, larynx, pharynx and nose or mouth (Acres and Kryger, 1981). A fixed UAO, intra or extrathoracic, is not changed by the phase of respiration. With a variable extrathoracic UAO the obstruction is worse during inspiration as the pressure inside the trachea falls on inspiration. Where as the extrathoracic upper airway is surrounded by atmospheric pressure, the intrathoracic upper airway is surrounded by pleural pressure which rises during forced expiration and hence exceeds the intratracheal pressure making a variable intrathoracic UAO worse during expiration (Acres and Kryger, 1981). The worsening of UAO during phases of respiration is reflected in the shape of the flow volume loop. Flow oscillations represented by a saw tooth pattern are occasionally observed and may represent a mechanical instability of the airway wall (Pellegrino et al., 2005).

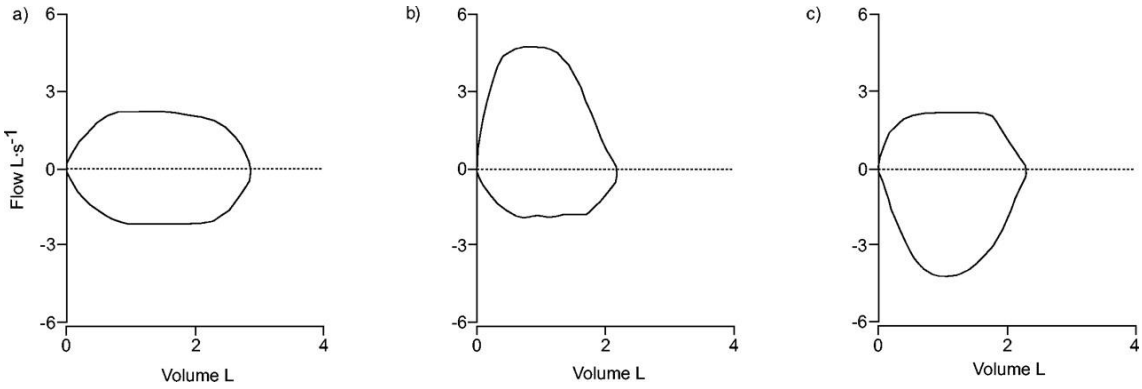

Figure 8: Flow volume loops: a.Fixed UAO b.Variable extrathoracic UAO c.Variable intrathoracic UAO

(Pellegrino et al., 2005)

Whilst the shape of the flow volume loop is most useful in the detection of UAO, some numerical indices are also helpful in the indication of UAO. Terminology varies between authors when reporting these indices, for example some refer to forced expiratory flow at 50% of FVC (FEF50) as maximum expiratory flow at 50% of FVC (MEF50) and likewise for inspiratory flows MIF50 for FIF50 which has to be considered when reading papers. This terminology is more pertinent

to the 25% and 75% values with the background to this variation being currently that the recommended measure is FEF when X% of the FVC has been expired (FEFX%) in contrast to the previous recommendation in Europe of use of MEF when X% of the FVC remains to be expired (MEFX%) (Miller et al., 2005b).
Lung function parameters aid in the differentiation of extrathoracic and intrathoracic obstruction as highlighted in figure 1; fixed extrathoracic UAO presents with decreased PEF, decreased MIF50 and MIF50/MEF50 ~1; variable extrathoracic UAO normal or decreased PEF, decreased MIF50 and MIF50/MEF50 <1; while intrathoracic UAO demonstrated decreased PEF, normal or decreased MIF50 and MIF50/MEF50 >1 (Pellegrino et al., 2005). With PEF being proportionally more affected than FEV1 in UAO, an increased ratio of FEV1/PEF >8ml/L/min should prompt flow volume loop examination (Pellegrino et al., 2005, Acres and Kryger, 1981). Although a figure of FEV1/PEF >8-8.5 ml/L/min is predominantly quoted, some studies have used a figure of up to >10 to indicate UAO (Acres and Kryger, 1981, Rotman et al., 1975). In addition to MIF50/MEF50 ratio, reduced MIF50, reduced PEF and FEV1/PEF >8ml/L/min indicating UAO, other numerical indices are also helpful indicators including FEV1/FEV0.5 >1.5, PIF <3L/s and PEF/MEF50 <2(Rotman et al., 1975, Mellisant et al., 1990, Acres and Kryger, 1981, Vincken et al., 1984, Herer et al., 2001).
Neuromuscular disorders, vocal cord dysfunction, sleep disorders, goitres, tumours, tracheal and post intubation stenosis, tracheomalacia, polychondritis, episodic laryngeal dyskinesia and laryngeal oedema are amongst a plethora of potential causes of upper airway obstruction and dysfunction. Thus accurate evaluation and characterisation of flow volume loops is vital in diagnosis and management (Vincken et al., 1984, Ramirez et al., 1986, Magnenat and Junod, 1991, Sterner et al., 2009, Tillie-Leblond et al., 1998, Blair et al., 1986).

2.3.4 Lung volumes

Spirometric measurements of inspired and expired lung volumes are very useful as highlighted above however, measurements of absolute lung volumes in certain circumstances are essential for accurate diagnoses (Pellegrino et al., 2005, Wanger et al., 2005). Different techniques of static lung volume measurement are available including nitrogen washout and helium dilution, but whole body plethysmography is the preferred technique. As previously

discussed, TLC calculation is required to accurately diagnose restrictive lung disorders and this can only be done by static lung volume measurements. Figure 9 illustrates static lung volumes and capacities on a volume-time spirogram of an inspiratory vital capacity (IVC) and shows total lung capacity (TLC), inspiratory capacity (IC), functional residual capacity (FRC), residual volume (RV), inspiratory reserve volume (IRV), tidal volume (TV) and expiratory reserve volume (ERV) (Wanger et al., 2005).

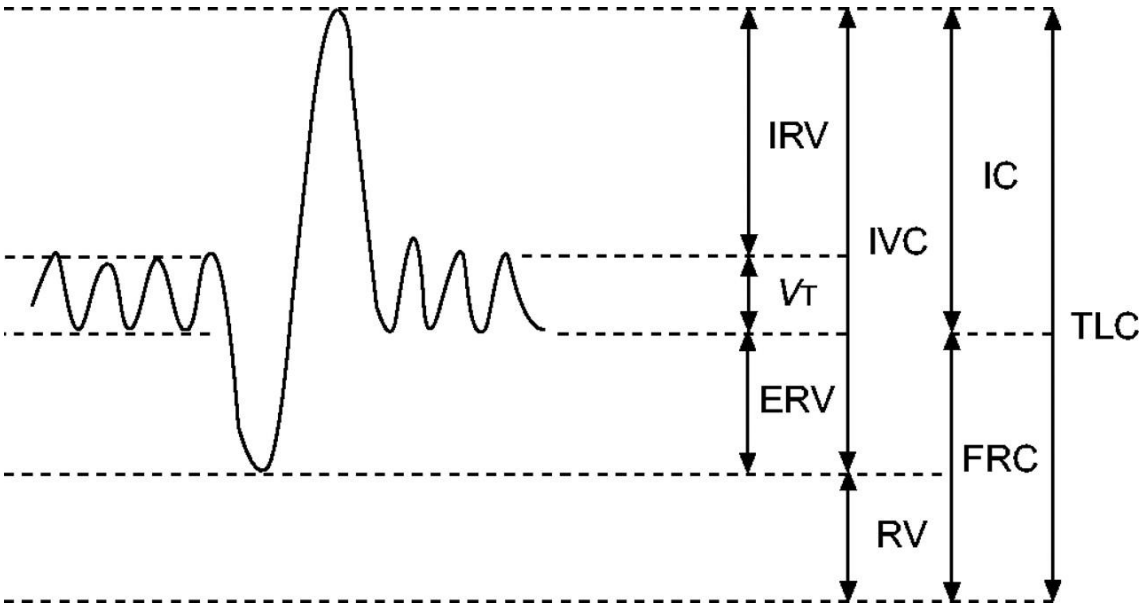

Figure 9: Static lung volumes and capacities

(Wanger et al., 2005).

TV is the volume of gas inhaled or exhaled during normal breathing, FRC is the volume of gas in the lung at the end of expiration during TV, ERV is the volume that can be exhaled from FRC, IC is the volume that can be inspired from FRC, RV is the volume of air remaining in the lungs after a maximal expiration and finally TLC is the total volume of air in the lungs after a maximal inspiration, i.e. the sum of the RV and vital capacity or can be considered the sum of the volume compartments (Wanger et al., 2005, Ranu et al., 2011).

Body plethysmography is based on Boyle's law stating that at a fixed temperature, pressure and volume of a given mass of gas are inversely proportional (Ranu et al., 2011, Criee et al., 2011). The patient sits inside an airtight box, inhales or exhales to a specified volume (usually FRC), and then a shutter drops across the breathing tube.

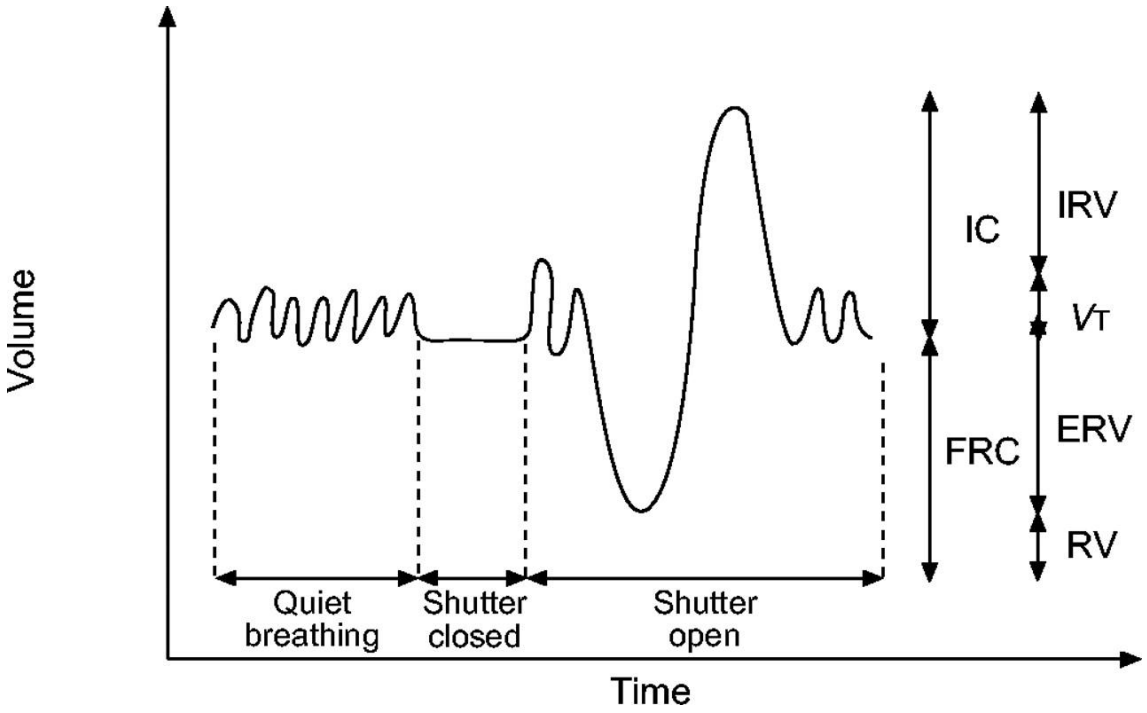

Figure 10: Volume-time display illustrating plethysmography sequence (Wanger et al., 2005)

In the measurement of FRC, the patient makes respiratory efforts against the closed shutter causing their chest volume to expand and reduce the box volume and thus increases the pressure in the box (Ranu et al., 2011). The volume is the FRC assessed by plethysmography which should be more correctly termed FRC_{PLETH} and it must be remembered that on occasions intrathoracic gas volume (ITGV) is used as a synonym for FRC_{PLETH} (Criee et al., 2011). When the shutter is reopened, ideally without resting between manoeuvres, the patient performs an ERV followed by a slow IVC manoeuvre (Wanger et al., 2005). These sequences allow measurement and derivation of lung volumes. Measurement of RV and TLC are essential in the accurate diagnosis of restrictive lung disorders characterised by a reduction in TLC, but are also very useful in diagnosing obstructive lung diseases where an increase in RV, suggesting air trapping, TLC or the RV/TLC ratio may suggest the presence of obstruction caused for example by asthma or emphysema (Pellegrino et al., 2005).

2.3.5 Diffusion capacity

The diffusing capacity of the lung for carbon monoxide (CO) is commonly abbreviated to DLCO and depending on country is also known as the transfer factor for carbon monoxide (TLCO). The test is primarily to assess how well

oxygen moves in an out of the lungs by measuring gas diffusion across the alveolar membrane. Gas diffusion is affected by the pulmonary vascular bed and the surface area and integrity of the alveolar membrane (Ranu et al., 2011). DLCO is normally reported as the absolute number and also when divided by alveolar volume (VA), the DLCO/VA, referred to as the transfer coefficient (KCO) (Kaminsky et al., 2007). KCO is most useful in interpretation of results, for example an individual who had had a pneumonectomy would have a falsely low DLCO if not corrected for VA as the remaining lung may be functioning normally. Neither KCO nor VA are constants and thus it must be remembered that the same DLCO can occur with different combinations of KCO and VA whilst at the same time suggesting different pathologies (Hughes and Pride, 2012). A critical part of diffusion capacity testing is the binding of CO to haemoglobin (Hb) and as such the presence of anaemia may decrease DLCO, or polycythaemia may increase DLCO thus correction equations are usually done to account for differences in Hb.

Diffusion capacity is measured by the single breath technique which involves measuring CO uptake over a breath hold phase. MacIntyre et al (2005), as part of the ATS/ERS task force series on standardisation of lung volume, review and discuss the technique of DLCO testing in great detail. The test system has a source of test gas, a method of measuring inspired and expired volume over time and gas analysers. The test gas comprises known concentrations of the CO and a tracer gas (commonly helium (He),) to measure VA, with the balance of the gas including oxygen (O_2) and nitrogen (N_2). With nose clip and mouthpiece in place the DLCO test begins with unforced exhalation to RV, the mouthpiece is connected to the test gas source and the patient inhales rapidly to TLC. It is important that the inspired volume is as close to known VC as possible and that inspiration is rapid. The patient then is asked to breath-hold for 10 ± 2 seconds prior to an unforced, smooth expiratory manoeuvre which should be less than 4 seconds. The DLCO calculations are then based on alveolar gas samples from the expired collected gases, with the first amount of gas from the physiological dead-space being discarded to collect a valid sample (Macintyre et al., 2005).

Large lung volumes, asthma and obesity are the commonest causes of a high DLCO, whilst polycythaemia, left-right shunt and pulmonary haemorrhage although causative are observed less frequently (Saydain et al., 2004).

Conditions that reduce one or more of volume of pulmonary capillary blood, membrane conductivity and CO-Hb chemical reaction rate can all lead to reduced DLCO including; anaemia, pulmonary emboli, emphysema, interstitial lung disease, pulmonary oedema, pulmonary vasculitis and pulmonary hypertension (Macintyre et al., 2005). Extrapulmonary reduction in lung inflation, for example respiratory muscle weakness, reduced effort or thoracic deformity, resulting in reduced VA can reduce DLCO and in this context highlights the importance of reviewing the KCO and clinical picture to form an appropriate diagnosis (Macintyre et al., 2005, Hughes and Pride, 2012, Siegler and Zorab, 1982, Hart et al., 2002).

2.3.6 Respiratory muscle function

Respiratory muscle function tests should be performed as part of a more comprehensive diagnostic process including examination, spirometry, lung volumes and diffusion capacity. Respiratory muscle dysfunction is to be differentiated from lung function abnormalities (Troosters et al., 2005). In generalised neuromuscular disorders it is unusual for the respiratory muscles to be unaffected (Polkey et al., 1995). Severe generalised respiratory muscle weakness manifests as breathlessness and tachypnoea, and when sufficiently severe nocturnal hypoventilation disturbs sleep, cognitive function and causes daytime somnolence (Polkey et al., 1995, Smith et al., 1988). The final sequelae are ventilatory failure and cor pulmonale (Polkey et al., 1995). Inspiratory muscle weakness can in part explain dyspnoea and poor exercise tolerance (Troosters et al., 2005). Expiratory muscle and bulbar weakness leads to speech problems and impairs cough and predisposes to mucus retention, pneumonia and aspiration (Troosters et al., 2005, Polkey et al., 1995). Poor respiratory muscle strength has been shown to be a predictive factor for mortality in both neuromuscular disease, for example ALS and non neuromuscular disorders such as congestive cardiac failure (Polkey et al., 2016, Meyer et al., 2001).

Respiratory muscle strength tests should be performed in those at risk of weakness, for example neuromuscular and metabolic disorders and in those with clinical signs and symptoms suggestive of respiratory muscle weakness; unexplained reduction in VC, Carbon dioxide (CO_2) retention (especially in the absence of airflow obstruction), orthopnoea, short sentences whilst speaking,

dyspnoea during bathing/swimming, tachypnoea, paradoxical abdominal and chest wall movements, problems with cough and recurrent infections and generalised muscle weakness (Troosters et al., 2005).

Respiratory muscles strength is generally measured by the pressures generated during inspiration or expiration and is commonly measured in either cm water pressure (cmH_2O) or kilopascals (kPa). Pressure is most commonly measured at the mouth and nose but can be further assessed by oesophageal, gastric and transdiaphragmatic pressures. The maximal expiratory pressure and maximal inspiratory pressure measured at the mouth are commonly abbreviated to MEP or PE_{max} and MIP or PI_{max} respectively. Sniff nasal inspiratory pressure (SNIP or P_{sniff}) measures inspiratory muscle function and being a natural manoeuvre can often be found easier to perform by many patients (Verin et al., 2001, Miller et al., 1985). Portable pressure meters facilitate easy bedside or departmental measurement.

The procedure must be explained clearly to the patient. Via a mouthpiece attached to the pressure meter, which is typically flanged, the patient performs the maximal effort manoeuvres and is asked to maintain the pressure. Multiple efforts are recorded, looking for reproducibility and the maximum pressure. Conventionally MIP is measured (Mueller manoeuvre) from RV and MEP (Valsalva manoeuvre) is measured from TLC (Polkey et al., 1995). The pressure maintained for at least one second, plateau pressure, is usually reported for MIP and MEP (Troosters et al., 2005). To measure SNIP a nasal plug is attached to the portable pressure device. Sniff nasal inspiratory pressure measurement is a simple procedure. From end expiration, a nasal plug is placed in one occluded nostril and a maximal sniff manoeuvre is performed through the contralateral nostril (Fitting, 2006, Heritier et al., 1994). In normal subjects maximal expiratory pressures are expected to be higher than inspiratory pressures, however SNIP results are generally higher than MIP results (Fitting, 2006, Troosters et al., 2005). This paradox is probably explained by the ease in which SNIP is performed compared to MIP and the subsequent more complete neuromuscular activation (Fitting, 2006). In patients with severe neuromuscular weakness, such as in advanced ALS, the SNIP manoeuvre can be more feasible and a determinant of VC (Fitting, 2006, Fitting et al., 1999, Stefanutti et al., 2000).

It is important that respiratory muscle testing is interpreted in the context of other pulmonary function tests as, with the exception of patients with severe neuromuscular disease in the advanced stages, respiratory muscle dysfunction does not correlate with lung function impairment (Troosters et al., 2005). It should be remembered that respiratory muscle test results must be interpreted with caution for a number of reasons. Patients may have had difficulty performing the tests for either physiological reasons or difficulty in understanding the instructions. If appropriate equipment or technique is not used, cheek and buccal muscles contribute to pressure generation and particular mouthpieces may result in additional leaks (Troosters et al., 2005, Koulouris et al., 1988). In the testing of inspiratory or expiratory muscles, the pressure is generated by all the muscles being tested and is, as such, not muscle specific. Furthermore, neuromuscular junction, muscle fibre, peripheral nerve, anterior horn, spinal cord or cerebral dysfunction may manifest as reduced respiratory muscle strength (Troosters et al., 2005).

2.3.7 Pulmonary function and ageing

In the majority of populations throughout the world life expectancy is increasing with a resultant increase in the population over the age of 65. The presence of disease will lead to functional decline and with advancing age comes reduced capacity to deal with disease. Ageing makes individuals more vulnerable as it is also associated with loss of protective mechanisms including a reduction in response to hypoxia and hypercapnia (Peterson et al., 1981). To distinguish from abnormal pathology it is important to understand the physiological changes that occur in normal ageing and their clinical manifestations. Changes in pulmonary function with ageing are important to appreciate particularly in areas such as anaesthesia in the elderly.

The lung matures to optimal function between the ages of 20 and 25 years, plateaus to age 35 and thereafter there is a progressive decline in lung function (Sharma and Goodwin, 2006). Ageing affects a number of parameters of lung function and thus ventilation, gas exchange and compliance. Ageing brings a reduction in chest wall compliance through changes to the thoracic cage. Calcification of the costal cartilages and chondrosternal junctions, osteoporotic height loss and kyphosis reduce the ability of the thoracic cage to expand (Estenne et al., 1985, Edge et al., 1964, Sharma and Goodwin, 2006).

Respiratory muscle strength and performance declines with age concomitantly with the geometric modifications (Janssens, 2005). Respiratory muscle, particularly diaphragmatic, strength decline may predispose older individuals to ventilatory failure during periods of increased ventilatory load on the respiratory system (Sharma and Goodwin, 2006). Respiratory muscle strength is related to both nutritional status and peripheral muscle strength which are important considerations in ageing (Enright et al., 1994, Enright et al., 1995).

The duration and range of possible inhaled pollutants creates a challenge in differentiating the effects of ageing versus environmental exposure on lung parenchyma (Janssens, 2005). The effects of ageing on the lungs have been described as similar to those that are seen in mild COPD, so called “senile emphysema” or “senile hyperinflation”. The changes seen in the ageing lung are homogenous rather than the irregular distribution seen in typical emphysema (Janssens, 2005). The change in the supporting structures within the lung parenchyma, with reduced recoil pressure of elastic fibres, causes distension of alveolar spaces, wider shallower alveoli and wider alveolar ducts (Verbeken et al., 1992, Kurozumi et al., 1994). As described, although these changes are histologically different from those seen in emphysema, the resulting change in lung compliance is similar (Janssens, 2005).

After the plateau stage in lung function, FEV1 and FVC decline with age. Whether this decline is linear or non-linear and accelerates with ageing is debated between evidence from cross-sectional and longitudinal studies (Dockery et al., 1985, Burrows et al., 1986). Given the changes described, an obstructive pattern may be seen in flow volume loops. Although PEF shows a tendency to decrease with age, there is substantial variability in predicted peak flow values and prediction equations that have to be considered (Enright et al., 2001, Bellia et al., 2003). Although TLC remains fairly constant, with the loss of elastic recoil of the lung parenchyma RV and FRC increase and VC decreases (Janssens, 2005, Sharma and Goodwin, 2006). Gas exchange also deteriorates with ageing with a declining DLCO contributed to by loss of alveolar surface area and change in the distribution of pulmonary blood flow (Butler and Kleinerman, 1970, Guenard and Marthan, 1996). Immunological changes also occur in addition to anatomical changes in ageing.

Extensive research in lung function in normal ageing, disease and populations has led to development of a large number of published reference equations.

Reliability in interpretation of lung function results in identifying normal from disease states relies on the selection of appropriate reference data. In the United Kingdom and throughout Europe the European Community for Steel and Coal reference is most widely used and accepted (Quanjer et al., 1993, Stanojevic et al., 2010).

2.3.8 Pulmonary function and neurodegenerative disease

Many neurological disorders can cause respiratory complications. Some manifest late in disease where as others may be an early sign. Unfortunately pulmonary complications are the leading cause of mortality in the majority of neurological disorders. The way each disease affects pulmonary function varies with the pathophysiology. Anatomically characterising the chronic neuromuscular disorders can be helpful in understanding this pathophysiology. Disorders that can affect the respiratory system include; cerebral cortex (stroke, neoplasm, seizures), brainstem/basal ganglia (Parkinson's disease, MSA, multiple sclerosis (MS), stroke, neoplasm, central alveolar hypoventilation, progressive bulbar palsy), spinal cord (trauma, infarction, haemorrhage, demyelination, syringomyelia), motor nerves/anterior horn cell (motor neuron disease (MND), ALS, spinal muscular atrophy, Charcot-Marie-Tooth disease), neuromuscular junction (myasthenia gravis, Lambert-Eaton syndrome, botulism) and myopathies/muscle (muscular dystrophies, polymyositis, dermatomyositis, mitochondrial myopathy, glycogen storage diseases) (Aboussouan, 2005, Benditt and Boitano, 2013).

In central neurological diseases, for example MS, abnormalities in central respiratory control may have a more direct role in the pathology of respiratory dysfunction (Aboussouan, 2005). Disorders that affect the corticospinal tracts, for example a mid-pontine stroke, can result in loss of voluntary breathing control due to the effect on the connection between the voluntary respiratory centres of the cortex and the spinal motor neurons (Benditt and Boitano, 2013, Schjolberg and Sunnerhagen, 2012). Extrapyramidal disorders can also affect voluntary breathing (Benditt and Boitano, 2013). Central hypoventilation syndrome, also known as Ondine's curse, may be congenital or acquired. Congenital cases are rare and disrupt autonomic but not voluntary breathing. Injury to the automatic respiratory centres causes central sleep apnoea on sleeping (Liess et al., 2008). Spinal cord pathology can affect ventilation

because of the direct influence on control of motor nerves controlling respiratory function (Benditt and Boitano, 2013).

In addition to respiratory muscles, neurological diseases can affect the bulbar muscles, the masticatory muscles and the larynx (Aboussouan, 2005). Respiratory muscle weakness (RMW) firstly causes sleep related hypoventilation and progresses to daytime respiratory failure. Particularly during rapid eye movement (REM) sleep, RMW can disrupt sleep by causing hypoventilation, apnoeas and hypopnoeas (Bourke, 2014). Irrespective of the primary diagnosis, a high prevalence of sleep disordered breathing has been reported in neuromuscular diseases (Bourke and Gibson, 2002). Difficulty with speech, swallowing and recurrent aspiration are sequelae of bulbar muscle weakness (Bourke, 2014). Sleep related hypoventilation also causes day time symptoms of sleepiness, lethargy, poor concentration and mood problems and if hypercapnia is present headaches can be a sequelae. Signs of RMW may include accessory muscle use, rapid shallow breathing, reduced chest expansion, reduced breath sounds, paradoxical abdominal movement, weak cough and weak sniff (Lyall et al., 2001b, Bourke and Gibson, 2002, Bourke, 2014).

Lung function, bulbar function and respiratory muscle strength are routinely monitored in a handful of neurodegenerative disorders, such as MND and Duchenne muscular dystrophy, however not in all. This may be a reflection of specific diseases not requiring pulmonary function monitoring but may also be due to a lack of research and evidence. Guidance issued by NICE, for the management of MND particularly highlights assessment and monitoring of respiratory function and consideration of non-invasive ventilation (NIV). Respiratory function monitoring in MND, with ALS being the most common subtype, is usually conducted every 2-3 months, however this may be adjusted dependent on the rate of decline. In MND any of the following should prompt respiratory review, with consideration of referral to the ventilation service, sleep studies and consideration for NIV; FVC or VC <50% predicted, FVC or VC <80% predicted plus any symptoms or signs of respiratory impairment, SNIP or MIP <40cmH_2O, SNIP or MIP <65cmH_2O for men or <55cmH_2O for women plus any signs or symptoms of respiratory impairment, SNIP or MIP rate of decline more than 10cmH_2O per 3 months, nocturnal hypoventilation, partial pressure of

carbon dioxide in arterial blood ($PaCO_2$) >6kPa or $PaCO_2$ <6kPa plus signs of respiratory impairment especially orthopnoea (NICE, 2016).

Type-II respiratory failure is the sequela of severe respiratory muscle weakness. Research suggests that NIV improves quality of life and extends life, particularly in non bulbar patients (Bourke et al., 2006, Lyall et al., 2001a, Mustfa et al., 2006). It is generally accepted that NIV should be offered to those with MND with daytime hypercapnia, however the occurrence of daytime hypercapnia can be a late sign in MND. In view of this, simple and accessible methods to predict nocturnal hypercapnia are very important particularly given the availability of, and time involved in performing, sleep studies (Murphy et al., 2010). In individuals without severe bulbar weakness, spirometry, MIP, MEP and SNIP should be used for monitoring progression. Compared with VC and MIP, SNIP is more sensitive in the prediction of daytime hypercapnia (Lyall et al., 2001b). The measurement of SNIP is also more sensitive to early RMW and a better predictor of death (Morgan et al., 2005). A fall in VC of >20% in the supine position is abnormal, is a marker of inspiratory muscle weakness and a good index of diaphragmatic function. Vital capacity also predicts survival (Allen et al., 1985, Bourke, 2014). In individuals with significant bulbar involvement, due to the difficulties in performing volitional lung function tests with the inability to form a tight lip seal around a mouthpiece, suboptimal results occur and tests of respiratory strength do not predict hypercapnia (Lyall et al., 2001b). In these individuals greater confidence is placed on results of oxygen saturations, blood gas analysis, transcutaneous pCO_2 and nocturnal oximetry and sleep studies (Bourke, 2014). The mortality and morbidity associated with pulmonary dysfunction in neurodegenerative disorders highlights the need for assessment and monitoring of lung function and respiratory muscle strength in these disorders.

2.3.9 Pulmonary function and Parkinson's disease

"He fetched his breath rather hard" was noted as a clinical feature by James Parkinson in his initial description of the disease in his 1817 essay on the shaking palsy (Parkinson, 1817). Despite this early recognition of respiratory involvement in PD little remains known and debate continues about the pattern of ventilatory dysfunction associated with the disease. Obstructive patterns, restrictive patterns, upper airway obstruction, respiratory muscle weakness and sleep breathing disorders have all been described but there is little consensus across the studies. Patterns of ventilatory dysfunction in previous research are summarised in table 3 below, however the complexity and variety of the techniques used and outcome measures in each study warrants significant further discussion.

Author, year	Number of patients	Pattern of dysfunction	MIP/SNIP	MEP	UAO	Effect of dopaminergic treatment
Neu et al, 1967	23 (10M, 13F) Parkinsonism	Obstructive	Reduced MIP	Reduced		
Paulson et al, 1970	22 Parkinsonism					MVV increased
Obenour et al, 1972	31 (18M, 13F) PD	11 Obstructive				Unchanged
Vincken et al, 1984	27 (19M, 8F) Extrapyramidal disorders				24 abnormal flow volume loops 10 UAO by author's criteria	
Tzelepis et al, 1988	9 PD	Normal	Normal MIP			
Hovestadt et al, 1989	31 (16M, 15F) PD	Normal	Reduced	Reduced	20-22 abnormal flow volume loops 18 had between 1-3 UAO parameters	
De Bruin et al, 1993	10 (8M, 2F)	Normal	Reduced	Reduced	off treatment 8 abnormal curves PEF reduced 2 fixed extrathoracic obstruction 1 intrathoracic obstruction	MEP and PIF increased (significant) MIP and PEF increased (moderate) Maximal flow volume curves improved

Izquierdo-Alonso et al, 1994	63 (39M, 24F)	85% Restrictive			49.2% pathological curves 21 type A 9 type B 1 obstructive 3 patients had at least 2 spirometric indices of UAO	
Sabate et al, 1996	58 (30M, 28F)	18 Obstructive 16 Restrictive	Reduced	Reduced	36 UAO on 3 spirometric indices	
Koseoglu et al, 1997	9 (4M, 5F)	1 Restrictive 1 Obstructive			4 UAO on 2 spirometric indices 1 type A curve 2 type B curve	
Canning et al, 1997	16 (13M, 3F)	Normal	Normal	Normal	16 curves with one or more abnormal features 10 UAO by author's criteria	
Vercueil et al, 1999	11 (5M, 6F)					Lengthening of inspiratory duration

Polati et al, 2001	21 (10M, 11F)	3 of 6 ex-smokers Obstructive 2 of 15 non-smokers Obstructive				
Herer et al, 2001	21 (14M, 7F)				5 patients had at least four UAO criteria	After levodopa 2 of the 5 met UAO criteria
De Pandis et al, 2002	12 (5M, 7F)	Restrictive				FEV1 and FVC improved in on state
Weiner et al, 2002	20 (10M, 10F)	Restrictive	Reduced	Reduced		FEV1 and FVC unchanged with treatment MIP and MEP increased with treatment (not significantly)
Cardoso et al, 2002	40 (21M, 19F)	Restrictive	Not reduced compared to control	Not reduced compared to control		
Maria et al, 2003	15 (12M, 3F)	Normal	Reduced	Reduced		
Haas et al, 2004	66 (47M, 19F)		Reduced	Reduced		
Sathyaprabha et al, 2005	35	33 Restrictive 2 Obstructive	Reduced	Reduced		FEV1, FVC, PEF, MIP, MEP improved in on state

Mikaelee et al, 2006	25 (19M, 6F)	13 Obstructive			1 UAO on authors criteria	
Silverman et al, 2006	28 (14M, 14F)		30.8% Low 69.2% Normal	71.4% Low 28.6% Normal		
Pal et al, 2007	53 (38M, 15F)	Restrictive	Reduced	Reduced		All PFT parameters improved with levodopa
Shaheen et al, 2009	30 (28M, 2F)	19 Restrictive 5 Obstructive				Improved in on state (not significant)
Seccombe et al, 2011	19 (17M, 2F)	16 Normal 2 Restrictive 1 Mild airflow limitation	13 (68%) Low	15 (79%) Low	Nil	
Guedes at al, 2012	26 (16M, 10F)		Reduced	Reduced		MIP and MEP not significantly improved in on state
Wang et al, 2014	30 PD (16M, 14F) 27 MSA (14M, 13F)	17 (56.7%) Restrictive 1 (3.3%) Central obstructive 13 (43.3%) Peripheric obstructive	Reduced	Reduced		

Table 3: Summary of the literature on pulmonary function in Parkinson's disease

Given the morbidity and mortality from pulmonary complications in PD, and the identification in 1817, it is surprising that Interest in pulmonary function tests in PD only seemed to begin in the late 1960's with the 1967 study by Neu et al, comprising 23 patients with Parkinsonism (Neu et al., 1967). The patients included had a diagnosis of Parkinsonism rather than IPD and no smoking history was documented. The measurement techniques, interpretation and reference values are different to those used currently. Notwithstanding this, the authors concluded the pattern was predominantly one of obstructive ventilatory defect based on the airway resistance being almost double the predicted values and more consistently present than any reduction in VC. This was heralded as precisely the pattern found in individuals with bronchial asthma or emphysema. They also commented on significant reductions in MIP, MEP, MIF and MEF and increasing dysfunction correlated with severity of disease. Parasympathetic hyperactivity was postulated as the cause of the obstructive pattern (Neu et al., 1967). A basic 1970 study of 22 patients with Parkinsonism, demonstrated an improvement in minute ventilatory volume (MVV) following administration of levodopa. Although change was seen in MVV, VC was not significantly altered following levodopa, however it must be noted that little detail was given about the participants including pre-existing lung disease and smoking history (Paulson and Tafrate, 1970).

Obenour et al, 1972, performed spirometry and plethysmography on 31 patients with PD and noted expiratory flow obstruction in 11 of the 31. In both the obstructed and non-obstructed groups increased RV and FRC were consistent with air trapping. Airway resistance (R_{AW}) was higher in the obstructed group and lung recoil at TLC was lower in this group also. The baseline lung function was assessed without the individuals on levodopa therapy. After 6 weeks of levodopa therapy all assessments were repeated and despite an improvement in neurological outcome measures there was no improvement in pulmonary function. Unfortunately smokers and individuals with known obstructive lung disease were not excluded from the study and whilst the authors concluded the air trapping was a result of neurologic effects of PD on chest wall mechanics, it is likely that the expiratory flow obstruction was a result of co-existing lung disease (Obenour et al., 1972)

Previous studies highlighting an obstructive ventilatory defect but no agreement on cause or site, led to interest in the involvement of upper airway musculature in airflow limitation in extrapyramidal disorders prompting a 1984 paper by Vincken et al. Spirometry, lung volumes, single-breath nitrogen wash out, MIP and MEP were performed in 27 patients with extrapyramidal disorders, of which 21 had IPD. Upper airway obstruction (UAO) was considered present when an increased helium response was accompanied by 2 or more abnormal flow ratios (FEV1/PEF >8.5ml/l/min or FEV1/FEV0.5 >1.5 or MEF50/MIF50 >1) and a PIF<3l/sec. A helium response and either abnormal ratios or reduced PIF sufficed for a diagnosis of UAO if the flow volume loop also showed a pattern of UAO. The patterns of UAO described on the flow-volume loops were categorised as either type A, respiratory flutter, with regular consecutive flow accelerations and decelerations or type B, irregular abrupt changes in flow often dropping to zero.

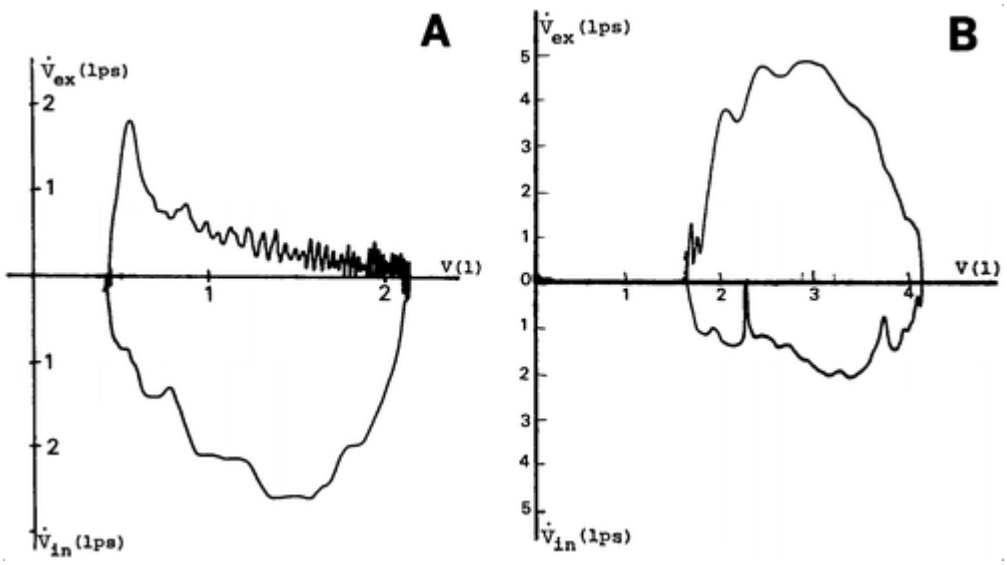

Figure 11: Flow-volume curves illustrating Type A and Type B pattern (Vincken et al., 1984)

Most commonly noted, in 24 of 27 (89%), was an abnormal flow volume loop pattern, with 18 type A and 6 type B patterns. Based on the authors UAO criteria above, 10 had UAO and it was noted that those with PD and UAO were more disabled by their disease, with higher Hoehn and Yahr scores than those without UAO. The proposed cause was that the intrinsic laryngeal muscles, and probably most of the other muscles surrounding the upper airway, are involved in the involuntary movements characteristic of extrapyramidal disorders and

airflow resistance is also exacerbated by contraction of upper airway muscles out of phase of those with the chest wall (Vincken et al., 1984)

Tzelepis et al, 1988, identified the lack of studies looking at respiratory muscle dysfunction and undertook a 9 person study in mild to moderate PD, with the benefit of a control group. In this small study there was no evidence of obstructive or restrictive dysfunction and it was concluded that while the patients were able to perform single respiratory efforts well, demonstrating normal lung volumes and MIP, they had problems performing repetitive inspiratory resistive-loaded ventilatory efforts associated with an increased oxygen cost of breathing and decreased efficiency compared to controls. Proposed mechanisms included altered neural drive to the muscles, alterations of muscle fibre composition and abnormal agonist-antagonist muscle activity (Tzelepis et al., 1988).

Prior to 1989, studies had predominantly included patients with mild disease which was highlighted by Hovestadt and Bogaard et al who studied pulmonary function in 31 patients with more advanced disease, at least Hoehn and Yahr III. They also excluded those with known lung disease or any structural upper airway abnormality. All patients were on levodopa and anticholinergic drugs. Interestingly, like the previous studies, there was heavy use of anticholinergic drugs in the management of PD. This is no longer standard practice. They reported a trend for most parameters to decrease with increasing Hoehn and Yahr stage. Significant differences between the means of the groups were only seen for the effort dependent variables of PIF, PEF, MIP and MEP, with MIP, MEP, PEF and MEF50 significantly below normal values. Forced inspiratory volume in 1 second, VC and FEV1/VC were relatively normal. This study was reported in two different papers and there was some inconsistency in reporting (Hovestadt et al., 1989, Bogaard et al., 1989). Both papers reported, according to the classification by Vincken et al, 4 patients had a type A flow-volume curve, however one paper reported 16 had a type B curve while the other reported 18 had a type B curve (Bogaard et al., 1989, Hovestadt et al., 1989, Vincken et al., 1984). The reason for this inconsistency was not apparent. The authors considered PIF, FEV1/PEF and MEF50/MIF50 to be indicators of UAO and reported 9 patients had an abnormal value for 1 parameter, 8 patients 2 and 1 patient all 3 parameters (Hovestadt et al., 1989). They hypothesized that muscle weakness and hypokinesia resulted in a lower and less explosive

muscle force which reflected the lower values of the effort dependent variables. Upper airway obstruction was a prominent feature, type A curves were assumed to be caused by tremor of the muscles of the upper airway and poor co-ordination of ventilatory system muscles, whilst type B curves were postulated to be predominantly due to muscle weakness (Bogaard et al., 1989, Hovestadt et al., 1989).

The effect of Parkinson's treatment on pulmonary function was considered in a 10 patient study by De Bruin et al in 1993. They assessed MIP, MEP, spirometry and maximal inspiratory and expiratory flow volume curves, in PD patients aged 42 to 60 years old, off treatment and repeated all measurements on treatment with apomorphine. Although an unusual study in current times, due to the young age of the participants and the dopaminergic medication of choice being apomorphine, the study yielded interesting results. Treatment improved neurological scores (modified Webster scale) however FVC off treatment was 84% predicted and did not change with treatment. Despite the relatively normal FEV1/FVC, only 2 of 10 patients had normal flow volume curves with the most common abnormality, both on and off treatment, being the increased volume expired before PEF achieved and absence of the sharp peak and resultant rapid decline in maximum expiratory flow. Off treatment MIP, MEP and PEF were all low with percent predicted values of 28.5%, 35.4% and 58.1% respectively and PIF was also low at 3.83L/s. On treatment significant improvements were seen in MEP (49.9% predicted) and PIF (4.37 L/s) and moderate improvements were seen in MIP (37.9% predicted) and PEF (70.0%) predicted. The study has to be interpreted with caution as there was no exclusion if patients had pre-existing respiratory disease. The authors concluded that PD patients have reductions in maximum flows and pressures during maximal efforts and these difficulties are improved with dopamine agonist treatment (de Bruin et al., 1993).

In 1994 Izquierdo-Alonso et al, undertook a larger study investigating pulmonary function in 63 patients with PD with maximal inspiratory and expiratory flow volume curves. There spirometric findings were in contrast to those found in previous studies with 54 patients (85%) having a FEV1/FVC ratio equal to or higher than 80% suggesting a restrictive element of pulmonary dysfunction. They also noted some weak but significant correlations between PD scales (UPDRS and Webster scales) and spirographic parameters, noting those with

more severe disease had lower FVC%, PIF and PEF and that those with motor fluctuations and or dyskinesia had lower FVC% and FEV1%. Thirty one (49.2%) had abnormal flow volume curves with 21 type A, 9 type B and 1 obstructive and 3 patients had 2 or more spirometric indices (FEV1/PEF, FEV1/FEV0.5, FEF50/FIF50) of UAO. Although the authors studied patients in Hoehn and Yahr categories I-V, again the results need to be interpreted with caution as 29 patients were treated with pergolide which is known to cause pleuropulmonary fibrosis which could show a restrictive pattern of spirometry. In addition the authors used FEV1/FVC to define restriction rather than TLC which would give far superior accuracy to results. Upper airway dysfunction and a restrictive pattern were heralded as the defining results and it was speculated that the restriction may be attributable to poor coordination or muscular rigidity limiting forced respiratory movements and also reduction in pulmonary compliance due to microatelectasias as a consequence of muscle dysfunction (Izquierdo-Alonso et al., 1994).

In 1996 Sabate et al, published a study of 58 patients that further complicated the picture of pulmonary dysfunction in PD by reporting a variety of dysfunctions. They undertook spirometry, lung volumes, airway resistance by body plethysmography, MIP and MEP in PD patients who had not received any dopaminergic medication for 8 hours prior to testing. Based on 3 spirometric indices (PIF <3 l/s, FEV1/PEF >8.5 l/min and MEF50/MIF50 >1) they reported 36 had evidence of UAO. Central obstruction or peripheral obstruction was seen in 18 patients and restrictive dysfunction was noted in 16 patients. Restrictive dysfunction was described as TLC <85% or FEV1/FVC >80% with FVC <80%, however the authors failed to publish the number with TLC <85%. Interestingly, they noted 16 patients had evidence of air trapping with RV >120% and RV/TLC >40% and 7 patients had a TLC >120% suggesting lung insufflation. Maximal inspiratory and expiratory mouth pressures were reduced and whilst FVC, FEV1 and FEV1/FVC% were all reported to be significantly below normal values the group means for these spirometric indices were all above 81% of predicted. An increase in the passive resistance to airflow (RAW) was also found, bradykinesia was higher in those with UAO, rigidity higher in those with obstruction and those with evidence of pulmonary dysfunction had evidence of impact on scores of activities of daily living. In summary evidence was reported that PD patients have a reduction in MIP and MEP and a high incidence of

restrictive and upper, central and peripheral obstructive patterns (Sabate et al., 1996a, Sabate et al., 1996b).

Pulmonary rehabilitation is a widely accepted and successful therapy for individuals with COPD with origins dating back to the middle of the 20th century (Casaburi, 2008). With this in mind it is somewhat surprising that there has been very little research on the effect of pulmonary rehabilitation in other disorders including PD where there has been documented evidence of pulmonary dysfunction. Koseoglu et al, 1997, with the knowledge that ventilatory and upper extremity exercise programs enhance maximal ventilatory capability and improve the effectiveness of ventilation during exercise, assessed 9 PD patients' pulmonary function and six-minute walk test (6MWT) before and after a 5 week exercise training programme as part of a comprehensive pulmonary rehabilitation programme (Koseoglu et al., 1997, Ries, 1994, Celli, 1994). Nine normal age matched control subjects also participated. The program comprised 60 minute sessions, 3 times per week for 5 weeks and included diaphragmatic breathing exercise, air-shifting techniques, voluntary isocapnoeic hyperpnea and unsupported upper extremity exercise. At baseline a spirometric restrictive defect was seen in 1 patient, obstructive defect in 1 patient (who was also a smoker) and 4 patients had evidence of UAO as judged by 2 spirometric indices (PEF and FEF50/FIF50). As may be expected, statistically significant differences were seen between the PD group and the control group on FVC, FEV1, FEF50, FEF25-75, MVV, PEF, PIF, IC, VC, FEF50/FIF50 and 6MWT with all values being lower in the PD group. When compared to baseline, a slight increase was seen at follow up in FVC, FEV1, FEF50, FEF25-75, PEF, PIF, VC, ERV, TV and MVV and a slight reduction seen in IC and respiratory rate, however these changes failed to reach statistical significance. A statistically significant increase was seen however in minute ventilation and 6MWT. Although the authors concluded this study suggested that exercise training in PD could decrease ventilatory requirements for a given workload, increase ventilatory muscle force and exercise tolerance and improve the effort dependent spirometry variables and ventilatory pattern during exercise, these results and conclusions should be interpreted with caution given the small number of participants, 2 of whom did not complete the study, and importantly the high use of anticholinergic medications which have a

large amount of systemic effects including on the respiratory system that can result in bronchodilation (Koseoglu et al., 1997).

Following Koseoglu et al's interest in the effect of upper extremity exercise on pulmonary function, Canning et al, 1997, sought to determine if abnormalities in respiratory function and gait affect exercise capacity. As part of this study they undertook spirometry, flow volume loops, lung volumes and mouth pressures in 16 participants with PD, Hoehn and Yahr stages I – III. Individual measurements of FEV1, FVC and FEV1/FVC were all normal and lung volumes did not indicate any obstructive or restrictive patterns. In contrast to previous studies, mean MIP and MEP were not significantly different to predicted values. In support of previous studies, PIF was significantly reduced and every subject's flow volume loop had at least one abnormal characteristic of a rounded off PEF, low PIF, high MEF50/MIF50 >1 and tremor. Ten patients fulfilled the criteria for UAO with FEV1/PEF <8.5ml/L/min, MEF50/MIF50 >1 and a PIF <80% predicted normal value. In this study the authors chose to use PIF<80% predicted normal value rather than the more commonly used PIF <3L/sec in the identification of UAO because they felt the latter failed to take into account variation in predicted normal values caused by height and gender. Interestingly they noted that while presence of UAO did not significantly correlate with percent predicted peak oxygen consumption achieved on maximal exercise testing, percent predicted PIF achieved did correlate with peak oxygen consumption. Noting the reduced flow rates, notably PIF, respiratory muscle weakness is often thought to contribute, however mouth pressures which were normal in this study provide only a global indication of respiratory muscle strength and may be altered by coordination of individual muscles. The authors concluded rather than weak inspiratory muscles in particular, it was more likely that flow rates and MIP would decrease because of poor coordination of respiratory muscles for a fast forceful manoeuver (Canning et al., 1997).

In 1999, identifying that little research had looked at breathing patterns at rest in PD, rather than forced manoeuvers, Vercueil et al undertook a small study, of 11 patients with IPD, focused on breathing patterns at rest both in the off state and then in the on state after administration of levodopa. The study had a number of limitations including size, akinetic rigid type patients only included and a number of patients exhibiting dyskinesia in the on state. The amount of ventilatory changes induced by levodopa varied massively among the patients,

however the most prominent effect on the pattern of breathing seemed to be an increase in the inspiratory duration. All patients reported levodopa alleviated any breathing discomfort. The authors concluded the larger change observed in the inspiratory rather than the expiratory duration was due to levodopa administration having more effect on those muscles with a high degree of postural function for example the external intercostals (Vercueil et al., 1999). These conclusions were reached based on the results of previous studies. Electromyography (EMG) of respiratory muscles in PD showed that the diaphragm exhibited a close to normal activity and other muscle showed a continuous activity that could be related to parkinsonian rigidity thus arguing in favour of unimpaired central respiratory rhythm generation (Petit and Delhez, 1961, Estenne et al., 1984). Findings by Rimmer et al, also supported this conclusion that when activated by postural movements the internal intercostals were strongly inhibited during inspiration but the external intercostals showed increases in inspiratory activity above and beyond that for postural muscular activity thus suggesting the internal intercostals (mainly active during expiration) provide a more ventilatory than postural role but vice versa for the external intercostals which have a more postural than ventilatory role (Rimmer et al., 1995).

As recently as the last decade, Pergolide with the potential to cause pulmonary fibrosis was still commonly used in the treatment of PD. In 2001 a study of pulmonary function in 21 PD patients was published by Polati et al, however in this study it has to be acknowledged that 15 of the 21 included were on Pergolide and 6 were also ex-smokers. They hypothesized that spirometric studies may serve as an indicator of patient's neurophysiological conditions. Spirometry was performed in 21 PD patients (Hoehn and Yahr I-III) and 16 healthy, age matched, non-smoker volunteers. Results showed 3 of 6 ex-smokers and 2 of 15 non-smokers had obstructive ventilatory defects however they defined this as FEV1/VC <89% predicted. They noted FEV1 and MEF25 were unsurprisingly decreased in the ex-smokers, however more noteworthy that MVV, PEF and MEF75 were significantly lower in the non-smoker PD group than the controls. There was a trend across the pulmonary function tests to deteriorate with advancing disease state, as defined by Hoehn and Yahr, with MVV best correlating with disease severity. Typically reduced in obstructive disease, MVV is usually preserved in restrictive disease and can be used as an

indicator in neuromuscular disorders that impair the strength and endurance of ventilatory muscles. Impairment of MVV in PD is likely as a result of bradykinesia and rigidity of respiratory muscles impairing repetitive motor tasks (Polatli et al., 2001).

With previous studies reporting a range in prevalence of UAO in PD and conflicting reports from Obenour et al and De Bruin et al with regards to the effect of dopaminergic medication on pulmonary function, Herer et al, 2001, published a study investigating the effects of levodopa on pulmonary function and specifically UAO. Spirometry and maximal inspiratory and expiratory flow volume curves were performed in 21 PD patients, Hoehn and Yahr II-IV, age range 52-89 years, 12 hours after withdrawal from anti parkinsonian drugs, then repeated after administration of placebo or weight dependent Co-beneldopa. The study was then repeated in all patients at 24 hours. The authors considered UAO to be present if at least 4 of the following 6 criteria were present; curve had a characteristic UAO saw-tooth sign, PIF <3L/s, FEV1/PEF >8.5mL/L/min, FEV1/FEV0.5 >1.5, FEF50/FIF50 >1 and a PEF/FEF50 <2. At baseline UAO was observed in 5 patients and after levodopa therapy 3 of these 5 no longer met the authors' criteria for UAO. Levodopa administration induced significant variations in PEF and the UAO ratios of FEV1/PEF and FEV1/FEV0.5. This study supported the hypothesis that levodopa improves lung function however the study was small, used levodopa doses that may have been insufficient in some patients and acknowledging that PEF measurements are subject to variability they failed to specify reproducibility criteria (Herer et al., 2001).

A brief paper published in 2002 by De Pandis et al further supported the finding of a restrictive pattern of pulmonary function in advanced PD. They performed spirometry and arterial blood gases (ABG) in the on and off states of 12 individuals with PD staged at least Hoehn and Yahr III. The authors concluded the spirometry results revealed a restrictive pattern in both the on and off states and that ABG analysis revealed normal values for PaO_2, $PaCO_2$ and pH in both the on and off states but a significant increase in $PaCO_2$ was seen in the off state (De Pandis et al., 2002). Although interesting, these results need to be interpreted with caution for a number of reasons; TLC was not measured and the presentation of the results in the publication in tabulated form did not include any units and by postulating the units it could be interpreted that PaO_2 was at

the lower end of normal and more importantly that the authors misinterpreted their on state spirometry results and it did not truly show restriction.

A further publication in 2002 by Weiner et al, reported spirometry, respiratory muscle strength and perception of dyspnoea in the on and off state of 20 individuals with PD, Hoehn and Yahr stages II-III and compared their results to 20 healthy, age and sex matched controls. They reported that predominantly patients had spirometry data indicating a mild restrictive pattern and that the mean FEV1 and FVC were not significantly different in the on and off states. Similar to previous studies the MIP and MEP in the off state were significantly reduced at 45% and 57% of predicted values respectively and although these values tended to improve in the on state the results were not statistically significant. Although using an uncommon technique to assess perception of dyspnoea, this was increased in the off state and improved in the on state, but despite this improvement those with PD reported more dyspnoea than controls. Close correlation was noted only between MIP and perception of dyspnoea in the off state. Although limited by size and technique, including no measurement of TLC, this study highlights dyspnoea, the pathophysiology of which is poorly understood. Weiner et al speculate that dyspnoea may be caused by a mismatch between incoming afferent information from airways, lungs, respiratory muscles and chest wall structure receptors and central respiratory motor activity, which may be similar to the sensory-motor disparity in limb muscles in PD (Weiner et al., 2002).

2002 brought a further publication of Brazilian data by Cardoso and Pereira. They reported spirometry and respiratory muscle strength tests of 40 PD patients, age 50 – 80, Hoehn and Yahr I-III, compared to 40 matched healthy controls. In support of studies in the same year a predominantly restrictive picture was reported noting a reduction in VC and FVC in the PD group, however in contrast to other studies there was no difference in MIP and MEP between the PD group and control group (Cardoso and Pereira, 2002). The breakdown in numbers for each Hoehn and Yahr group were not stated thus if predominantly early disease no difference in mouth pressures may have been observed. Basing a diagnosis of restriction on FEV1 and FVC measurements without measuring TLC, raises questions about the validity of data as poor technique by the investigator or patient, or submaximal effort, can produce results with FEV1 and FVC readings consistent with false positive restriction.

As part of a wider study into sleep breathing disorders in PD, Maria et al, 2003, reported basic spirometry, MIP and MEP in 15 PD patients and 15 matched healthy controls. FEV1, FVC and FEV1/FVC were normal in both groups, however median values for MIP and MEP were significantly reduced, 55% predicted and 45% predicted respectively, in the PD group (Maria et al., 2003). The study did not exclude ex-smokers and also predominantly included those with mild disease severity which the authors based on UPDRS scores, rather than Hoehn and Yahr stage, which makes the study difficult to compare with others.

Whilst not publishing exact figures, Haas et al's 2004 study focussed on respiratory muscle strength tests yielded interesting results. Respiratory mouth pressures, activities of daily living, activity levels and quality of life questionnaires, peak heart rate, peak oxygen consumption, lactate thresholds and stages completed on a cycle ergometer test were recorded in 66 participants with PD and 32 age-matched healthy controls. Whilst MIP and MEP were found to be significantly lower in the PD group this did not affect the results of the questionnaires but did correlate with lactate thresholds and ergometer stages completed. With an average Hoehn and Yahr stage of 2, this study supported a weakness of respiratory muscles in mild to moderate PD, which seemed to affect individuals during exercise but not during tasks that required a smaller effort, for example activities of daily living (Haas et al., 2004). The strength of skeletal muscles was not measured during this study and given the positive findings at ergometer stages and lactate threshold, a contribution by limb weakness cannot be excluded. Nonetheless, the results remain relevant as previous studies have shown that whole body exercise training has the potential to improve respiratory muscles, improving inspiratory muscle strength has benefited other patient groups and athletes and can be safely done in patients with neuromuscular disorders (Enright et al., Rutchik et al., 1998, Sánchez Riera et al., 2001, Cahalin et al., 1997, McCool and Tzelepis, 1995, Koessler et al., 2001, Powers and Criswell, 1996).

With this interest in inspiratory muscle training Inzelberg et al, 2005, measured respiratory muscle strength and endurance, perception of dyspnoea and quality of life in 20 PD patients, Hoehn and Yahr stages II-III. The patients were then divided into 2 groups of 10, 1 group received 12 weeks of ½ hour, 6 times per week specific inspiratory muscle training and the other group received sham

training. Significant improvements in inspiratory muscle strength, endurance and perception of dyspnoea were seen only in the intervention group, MIP increased from a mean of 62.0 to 78.0 cmH_2O (Inzelberg et al., 2005). Despite the small size of the study this highlights a potential role for inspiratory muscle training in PD.

With the afore lack of clarity and conflicting reports on the effect of dopaminergic medication on pulmonary function, Sathyaprabha et al, researched this further in a study published in 2005. Spirometry, respiratory muscle strength and MVV were performed in the off and on states (after levodopa therapy) on 35 PD patients and 35 healthy age-matched controls. At baseline they reported the PD group had significantly lower FEV1, FVC, PEF, MVV, MIP and MEP compared to the controls and 33 of 35 PD patients showed restrictive spirometry and 2 obstructive. Following administration of levodopa all the above indices significantly improved (Sathyaprabha et al., 2005). The results of this study, although supporting studies in the same era that the predominant pattern of spirometric dysfunction was restrictive, need to be interpreted with caution; lung volumes with TLC were not measured and hence not contributory to a diagnosis of restriction, the mean age in the PD group was only 53 and 32 patients were Hoehn and Yahr stage II and 3 stage I, thus earlier disease than other studies. Although the authors felt the restrictive pattern of pulmonary dysfunction demonstrated was probably due to abnormally low chest wall compliance secondary to rigidity, I suspect that given the patient demographics these results more likely represent a false positive finding of restriction due to poor spirometry technique.

Previous studies had predominantly used spirometry alone rather than including body plethysmography for assessment of lung volumes. A small study based in Iran, Mikaelee et al 2006, undertook lung function testing including body plethysmographic measurements of lung volumes in 25 PD patients, Hoehn and Yahr I-V, mean age 63.8 ± 11.1 and compared to 20 control subjects. In the PD group an obstructive pattern of respiratory dysfunction was found in 13 (52%) and evidence of air trapping in 56% with a markedly raised RV. In contrast to previous studies no evidence of restrictive spirometry was found and only 1 in the PD group had evidence of UAO (based on abnormal PIF and FEV1/PEF). Although there was a trend towards a correlation between increasing Hoehn and Yahr scores and abnormal pulmonary function, this was not statistically

significant (Mikaelee et al., 2006). Despite use of this methodology, the small numbers in the study and attempts to further sub analyse data based on each Hoehn and Yahr group led to results lacking statistical significance.

An eminent American group in the field of speech and language therapy, including authors Erin Silverman and Christine Sapienza, published a study on mouth pressures in 2006 in 28 PD patients, mean age 64, Hoehn and Yahr stages II-III. MIP was less impaired than MEP when compared to controls, 69.2% of MIP measurements were within or above normal as opposed to only 28.6% of MEP measurements being within normal range. Whilst their MEP findings supported previous studies, their MIP findings contrasted. The authors acknowledged potential difficulties in comparing studies including clinician measurement technique and pharmacological differences, however hypothesized interesting possible reasons for the apparent difference in the responses of the inspiratory and expiratory muscles (Silverman et al., 2006). The inspiratory and expiratory muscles assume different roles within the breathing cycle; during tidal volume breathing the inspiratory muscles have constant activation (e.g. the scalenes and parasternal intercostals are always active during quiet breathing), however abdominal/expiratory muscles play less of a role because expiration during tidal volume breathing is due to passive recoil (De Troyer and Estenne, 1984). It is feasible that in the presence of disease the inspiratory muscles may lose less strength than the expiratory muscles due to baseline EMG activity of inspiratory muscles always being greater than that of expiratory muscles during quiet breathing (Silverman et al., 2006).

Members of the same group from the National Institute of Mental Health and Neurosciences in Bangalore who published a 35 patient study in 2005, reported a further study in 53 patients in 2007. Pal et al, assessed spirometry, MIP and MEP in the off state and the on state (after levodopa administration) in PD patients Hoehn and Yahr II-IV (predominantly stage II) with a mean duration of PD of 3.1 years, as compared to 53 healthy age matched controls. They did not publish if these participants included those from the previous study. Nineteen of the PD group were smokers and 5 of the control group, with all smokers being male. Whilst spirometry was measured with standardised commercially available equipment, the pressure monitor used to measure MIP and MEP was fabricated. They concluded the pattern of pulmonary dysfunction in the PD

group was restrictive however did not publish exact numbers and they noted a significant impairment in FEV1, FVC, PEF, MVV, MEP and MIP in both the off and on state in the PD group compared to the controls. All PFT parameters improved with levodopa but remained worse than the control group.
Interestingly they recorded the percent predicted values of FVC, FEV1, MVV, MIP and MEP to be significantly lower in women than men in the PD group only. Although there were several correlations between PFT parameters and UPDRS motor subscores these did not reach statistical significance likely due to the low numbers in the study (Pal et al., 2007). Whilst an interesting study it was limited by use of fabricated rather than standardised equipment, low numbers, lack of lung volumes assessed by body plethysmography and over 35% of the group being smokers.
A further 2 years passed without any significant publications pertaining to pulmonary function in IPD. In 2009, Shaheen et al published a basic spirometry study of 30 patients with IPD, mean age 67.7 years, mean disease duration 3 years, with 77% tremor dominant disease and 23% presenting mainly with akinesia. Pulmonary function tests comprised FEV1 and FVC in the off and on states (after levodopa) compared to a 15 participant age and sex matched control group. They concluded, similar to Pal et al above, the pattern of dysfunction was predominantly restrictive, with a restrictive defect observed in 19 (63.3%) and an obstructive defect observed in 5 (16.7%) of PD patients. Thus 80% had abnormal spirometry and whilst they noted pulmonary function parameters improved with levodopa treatment, the improvement did not reach statistical significance (Shaheen H.A., 2009). Although supporting the findings of studies conducted in proximity, the small numbers and simplicity of the study unfortunately lessen its impact.
Identifying that respiratory involvement in PD could potentially occur through more than one mechanism, i.e. peripheral or central, Seccombe et al undertook a 19 patient study, published in 2011, to identify further evidence of abnormal ventilatory control in PD. With the Braak hypothesis suggesting the earliest evidence of the disease is in the medulla, enteric nervous system and olfactory bulb then slowly spreading to the mid-brain and finally to the cortex, this raises the question that medullary (brain stem) ventilatory control could be affected in PD (Braak et al., 2004). Predominantly lung function studies have looked at peripheral motor manifestations such as tremor or rigidity affecting lung function

rather than the effect brain stem involvement has on respiratory control. Seccombe et al, measured spirometry, lung volumes (body plethysmography), respiratory muscle strength, response to hypoxic gas inhalation and hypercapnic ventilatory response and occlusion pressure in 19 patients with PD in the on state. Normal lung function was observed in 16, mild airflow limitation in 1 and 2 were restrictive based on TLC. No flow volume loops were consistent with upper airway obstruction. MIP and MEP were reduced in 68% and 78% of patients respectively. Four patients were unable to maintain an adequate seal to complete the hypercapnic ventilatory response (which was abnormal in 47%) and occlusion pressure (which was abnormal in 73%). Most subjects had normal ABGs before and following the altitude simulation test. The authors demonstrated impaired respiratory drive in response to hypercapnia and the abnormal occlusion pressure response indicated central drive impairment, however it has to be remembered that respiratory muscle myopathy may have an inhibitory effect on this central measure and it is possible that reduced respiratory muscle strength contributed in some way to the abnormal response observed (Seccombe et al., 2011). While a comprehensive battery of tests were undertaken in this study, the Hoehn and Yahr stages were I-III with 3 participants unclassified and the medication usage was very varied with 19 taking levodopa/carbidopa, 11 on dopamine agonists (9 pramipexole, 2 cabergoline, 1 overnight apomorphine), 10 on entacapone (COMT inhibitor), 2 on amantadine and 1 had undergone deep brain stimulation. With all these variables and a small number of participants, the results are difficult to interpret. In 2012 Guedes et el, published a limited study focussed on MIP and MEP in 26 patients with PD, age range 50 – 75, Hoehn and Yahr II-III compared to 26 gender age matched controls. The PD group had measurements in the on and off states. In support of previous studies MIP and MEP in PD in both the on and off states were lower than the control group. This failed to reach significance in the female PD MIP results. In contrast to previous studies, with the exception of PD female MEP results, any change in respiratory muscle strength in the on and off states failed to reach statistical significance. Given their results that dopamine replacement had little impact on the measured respiratory parameters, the authors proposed that respiratory dysfunction in PD may be unrelated to dopaminergic dysfunction (Guedes et al., 2012). I suspect this may prove to be inaccurate with the original small number in the study and the

dichotomising of results in already small numbers leading to a lack of statistical significance.

Finally, identifying the limited pulmonary function comparative data in PD and healthy subjects, and even more limited data between different parkinsonian disorders, Wang et al, 2014, compared spirometry, lung volumes (body plethysmography), DLCO, MIP and MEP in PD, MSA and healthy subjects. They tested 30 PD (mean age 61.8, mean disease duration 4.9 years), 27 MSA (mean age 59.85, mean disease duration 3.63 years) and 20 healthy elderly controls (mean age 60.85). Hoehn and Yahr stage was II-V for the PD group and the MSA group comprised 20 probable and 7 possible MSA. Spirometry showed a restrictive pattern in 56.7% of PD patients (63% MSA), central obstructive in 3.3% PD (0% MSA) and peripheric obstructive pattern in 43.3% of PD (29.6% MSA). Compared to controls, both PD and MSA groups had lower VC and higher RV, while there were no significant differences in TLC between the groups. In both the PD and MSA groups, VC, FEV1 and FVC decreased and MIP and MEP decreased markedly. Interestingly DLCO was only notably reduced in the MSA group. In PD patients, VC, FVC, FEV1, PEF, MIP and MEP all negatively correlated with UPDRS-III motor section, concluding the more seriously the patient is affected by motor symptoms, rather than the disease duration, has the greater influence on pulmonary function (Wang et al., 2014). When reviewing this study, the authors based the conclusion of restrictive dysfunction in this Chinese PD population on the results of spirometric tests and not TLC. From the graphical representation of TLC it would appear that the mean percentage predicted TLC was above 80% in all groups which would indicate an alternative conclusion. This study highlights the need for further research into pulmonary function in all parkinsonian syndromes.

This comprehensive literature review of pulmonary function in PD, highlights the small number of studies, with small numbers of participants and the disparity in results and conclusions. Aside from the numbers involved, the reviewed studies have a number of factors that must be taken into account; varying age groups, different Hoehn and Yahr stages and varying definitions of PD. The selection of antiparkinsonian medication used across the studies is vast, including a number of drug groups, or individual drugs, that are no longer commonly used predominantly due to their side effects. The studies reviewed did not consistently use standardised equipment and definitions in pulmonary function

testing and presumably due to availability, the majority lacked measurement of lung volumes by body plethysmography resulting in patterns of dysfunction being determined by spirometry alone which can lead to interpretive errors particularly in restrictive dysfunction. These findings highlight the need for significant further research using gold standard techniques to assess pulmonary function in PD and the parkinsonian syndromes.

2.4 Cardiorespiratory fitness

Cardiorespiratory fitness describes the ability of the circulatory and respiratory systems to supply oxygen to muscles during sustained physical activity. The system needs to be able to adapt and respond when demand increases, such as during exercise. Exercise induces short term and long term effects on the cardiorespiratory system. When exercise commences the pulmonary ventilation needs to increase and the cardiovascular system is required to predictably respond proportional to the skeletal muscle oxygen demands.

Pulmonary ventilation primarily increases due to stimulation of the respiratory centres in the brain stem from the motor cortex and feedback from the proprioceptors in the active muscles and joints. In normal untrained adults this can range from 10L/min at rest to over 100L/min on maximal exercise and in highly trained, large, male athletes over 200L/min at maximum (Manley, 1996). Cardiac output (Q_T) is the volume of blood the heart pumps out in one minute and is the product of the stroke volume (SV) ,which is the amount of blood pumped out per beat, and the number of heart beats per minute (heart rate (HR)) (Vincent, 2008). The arterial-venous oxygen difference (a-vO2 diff) is the difference between the oxygen concentration of the arterial and mixed venous blood (Manley, 1996). An individual's aerobic capacity or maximum oxygen uptake (VO2max) is a function of, and thus limited by, the ability of the cardiovascular system to supply (Q_T) and/or the skeletal muscles to use (a-vO2 diff) oxygen (Manley, 1996, Jakovljevic et al., 2012b).

As work increases the Q_T increases in an almost linear pattern up to a maximum. This occurs due to increases in HR and SV (Manley, 1996). Although both HR and SV increase with exertion, the contribution to the increase Q_T is much greater from the increase in HR particularly at high exertion (Higginbotham et al., 1986). Maximal achievable heart rate

(HRmax) is related to age and although there are numerous prediction equations, HRmax = 220-age is commonly accepted and used (Robergs and Landwher, 2002). During exercise, blood flow changes with more blood being sent to skeletal muscles, and as temperature rises to the skin. Mean arterial pressure increases in response to exercise, predominantly due to a rise in systolic blood pressure while diastolic blood pressure remains near resting levels. In normotensive individuals systolic blood pressure rises linearly peaking at maximum between 200 to 240 mmHg (Manley, 1996). After exercise, blood pressure drops below pre-exercise resting levels in an aptly named phenomenon called post-exercise hypotension. Whilst this mechanism is caused largely by decreased vascular resistance many aspects remain misunderstood (Halliwill et al., 2013). During increasing work the a-vO2 diff increases as a result of increased oxygen extraction from arterial blood as it passes through exercising muscle. Coronary blood flow increases during exercise due to an increase in perfusion pressure of the coronary artery and from coronary vasodilation (Manley, 1996).

While exercise produces short term responses to meet immediate demand, exercise training produces long term adaptations. These adaptations are not purely limited to cardiovascular, respiratory and skeletal muscles but also include bone, metabolic and hormonal adaptations. The magnitude of these adaptations depends on a number of factors including pre-exercise fitness level, type of exercise programme, intensity and duration for example. After endurance training, SV is increased at rest and during submaximal and maximal exercise, whilst HR is decreased at rest and during submaximal exercise and unchanged at maximal work rates. Training increases plasma volume and end diastolic volume and results in more elastic recoil. Long term responses also include hypertrophy of cardiac muscle fibres and reduction in blood pressure. Respiratory adaptations with training are predominantly an increase in pulmonary ventilation and an increase in pulmonary diffusion during maximal exertion. Dependent on training modality, skeletal muscles undergo fiber hypertrophy and hyperplasia and increased recruitment (Manley, 1996). Endurance training also facilitates a greater capacity for blood flow in skeletal muscles by increasing the numbers of capillaries (Prior et al., 2004).

The most widely accepted measure of cardiorespiratory fitness or aerobic capacity is peak oxygen consumption (VO2peak). As alluded to above, although

VO2peak and VO2max are often used interchangeably there is an important distinction in that VO2peak is the highest value achieved on a particular test where as VO2max refers to the highest value that is considered to be attainable by an individual.

2.4.1 Quantification of cardiorespiratory fitness

There are a number of commonly used surrogate measures of cardiorespiratory fitness for example; the six minute walk test (6MWT), which is the distance an individual covers when walking for 6 minutes on a measured track, the multi-stage fitness test (also known as the beep test or pacer test) and motion sensors. The gold standard measure of cardiorespiratory fitness is peak oxygen uptake (VO2peak), usually measured during large muscle dynamic activity such as running or cycling. Although the gold standard, this technique is not always readily available as it requires trained operators and relatively expensive equipment. The most common modalities for clinical testing are the treadmill or cycle ergometer. Stationary cycle ergometers are particularly useful in groups where use of the treadmill may be hazardous. Individuals with significant gait abnormalities, including PD where problems can occur with freezing of gait, are safer using a cycle ergometer. It has to be remembered that stationary cycling may be an unfamiliar activity to some individuals and the exercise test may end prematurely, usually due to localised leg fatigue, with resultant lower values in VO2peak as compared to treadmill testing (Hambrecht et al., 1992, Myers et al., 1991).

VO2peak is the most accurate measurement of functional capacity and an indicator of overall cardiopulmonary health (ATS/ACCP, 2003). During an exercise test, blood pressure and continuous electrocardiogram (ECG) and expired gas composition, oxygen (O_2) and carbon dioxide (CO_2), are measured. VO2max is achieved when oxygen consumption remains plateaued at a steady state despite increasing workload. The exercise test protocol selected should consider the purpose, outcomes desired, and characteristics of the group or individual being tested, e.g. age, disease and symptomology (ACSM, 2010). The most familiar and common protocol is the Bruce protocol for treadmill testing which uses relatively large increments (metabolic equivalents (METS) or watts) every 3 minutes. The Ellestad protocol also uses large increments, where the Naughton or Balke-Ware protocols use smaller increments. With larger

increments changes in physiological response tend to be less uniform and these protocols tend to be better suited to younger or more physically active individuals. Protocols with smaller increments or alternative ramp protocols are preferable for those who are older, deconditioned or with chronic diseases (ACSM, 2010). Rather than incremental increases, in ramp protocols the work rate increases in a constant and continuous manner (Kaminsky and Whaley, 1998, Myers et al., 1992, Myers et al., 1991). The increasingly popular ramp protocols are advantageous as they avoid large unequal increments in workload, there is uniform increase in haemodynamic and physiologic responses, the protocol can be individualised and most importantly they offer more accurate estimates of ventilatory thresholds and exercise capacity (Myers et al., 1991). When an exercise test is completed, and the individual is in the post exercise period, monitoring must continue for at least 5 minutes or until any ECG changes return to baseline and any symptoms resolve and heart rate and blood pressure return to near baseline (ACSM, 2010).

As discussed, whilst dependent on a number of factors, absolute VO2max levels are typically higher in males than females. As a guide, an untrained healthy male may have a VO2max of 35-40 ml/kg/min (Guyton and Hall, 2011). The highest VO2max results tend to be seen in elite endurance sportspersons, for example runners, rowers and cyclists, with values in the most elite approaching 100ml/kg/min. To highlight these exceptional VO2max results in the top elite athletes, thoroughbred racehorses exercising on an inclined treadmill were recorded as demonstrating VO2max results of 131-153 ml/kg/min (Rose et al., 1988).

While predominantly discussing VO2max, it is important to mention, as above, the concept of metabolic equivalents or METS. One MET is the amount of oxygen consumed sitting at rest and is equal to 3.5ml O_2 per kg body weight and as such, the energy cost of an activity can be calculated by dividing the relative O_2 cost of the activity in ml/kg/min by 3.5. The MET concept provides a simple technique to describe functional capacity and with known energy expenditure values, in METS and watt units, for household task and recreational activities allows simple visual imagery of energy expenditure (Jette et al., 1990).

2.4.2 Cardiorespiratory fitness and ageing

Ageing, including in the absence of disease, is associated with a progressive decline in cardiorespiratory fitness, or VO2max, and a resultant reduction in capacity for physical activity. As an individual's aerobic capacity or VO2max is a function of, and thus limited by, the ability of the cardiovascular system to supply (QT) and/or the skeletal muscles to use (a-vO2 diff) oxygen, it stands to reason that ageing's effects on these factors are causative in the decline. Until late middle age, reduced cardiac output and possible maldistribution of cardiac output play a dominant role in reductions in oxygen delivery (Betik and Hepple, 2008). As demonstrated by maximal heart rate prediction equations, maximal heart rate achievable declines with age which contributes to decreased cardiac output. Sarcopenia, a degenerative loss of skeletal muscle mass and strength, is associated with ageing. Ageing, particularly extreme old age, is also associated with a decline in skeletal muscle oxidative capacity, due in part to mitochondrial dysfunction, but interestingly the structure of the capillary bed does not appear to decline in a way that would affect the capacity for oxygen diffusion (Betik and Hepple, 2008). Although a small study, and older subjects having an average age of 58, Kim et al concluded muscle mass is associated with VO2max however it appeared that VO2max was less influenced by muscle mass in older subjects than in younger subjects (Kim et al., 2016).

Despite the effects of ageing, in older persons aerobic exercise training can improve VO2max. This was demonstrated in a 41 trial meta-analysis of studies including 2012 older subjects (within-group mean age of 60 years and older), reporting greater improvement in VO2max to be associated with training length greater than 20 weeks and intensity between 60-70% of VO2max (Huang et al., 2005). With cardiorespiratory fitness associated with cardiovascular and all cause mortality this highlights the protective benefits available by improving aerobic capacity in older adults.

2.4.3 Cardiorespiratory fitness and neurodegenerative disease

Neurodegenerative disease is a somewhat umbrella term for a range of diseases that affect the neurons. These include diseases such as PD, Parkinson's plus syndromes, Alzheimer's, Amyotrophic Lateral Sclerosis (ALS), Huntington's, spinal muscular atrophy, spinocerebellar ataxias and prion disease. Despite being grouped together, these disorders are markedly different

and affect cellular, physiological and cognitive function in different ways that all may affect cardiorespiratory fitness. There is a body of evidence that suggests physical activity and higher cardiorespiratory fitness levels can delay the onset and reduce the morbidity associated with neurodegenerative diseases (Scarmeas et al., 2011, Ahlskog, 2011, Archer et al., 2011).

Even in early stage ALS, with skeletal muscle mass similar to normal, research demonstrates a reduction in VO2peak (Mezzani et al., 2012). In Alzheimer's type dementia (AD) cardiorespiratory fitness is lower than normal subjects, including in early disease. Lower cardiorespiratory fitness in AD is associated with progression of dementia severity and brain atrophy, indicating a link between progression of dementia severity and cardiopulmonary health. In non-demented subjects there is also a trend for lower aerobic capacity to be related to cognitive decline (Vidoni et al., 2012).

The evidence, although vast, highlighting impaired cardiorespiratory fitness in neurodegenerative disorders, also highlights the potential morbidity and mortality benefits from improving cardiorespiratory fitness, particularly in cognitive function which supports the neuroplasticity effects of exercise.

2.4.4 Cardiorespiratory fitness and Parkinson's disease

Advancing PD and increased severity of disease are associated with reduced physical activity and a more sedentary lifestyle. A recent review of exercise and parkinsonism underlined the improvements pertaining to both the functional deficits and neurological biomarker manifestations of the disorder and concluded that physical exercise co-administered with antiparkinsonian medication ought to contribute to an enrichment of aspects of functioning and the quality of life of PD patients (Archer et al., 2011). The review however mentioned little evidence of the effect of exercise on aerobic capacity in PD and literature review has found this area to be lacking in high quality studies. A number of studies used estimates of V02max, for example based on heart rate, rather than actually measuring it, or used surrogate markers of aerobic capacity. For a measure to be valid it needs to be reliable and repeatable in the proposed subject population, thus a "gold standard" measure must be highly reproducible in repeated measurements obtained from the same subject under the same circumstances and must show little within-subject variation. Katzel et al, measured VO2peak in 70 individuals with PD (Hoehn and Yahr stages 1.5 to 3)

on a maximal effort treadmill test. A second test was performed a week later in all 70, and a further week later a third test was performed in 21. Their results demonstrated measurement of VO2peak in PD was reliable and repeatable with an intraclass correlation coefficient (ICC) of 0.90 for VO2 peak in ml/kg/min. Maximum heart rate and final speed achieved were also highly reliable with ICCs of 0.91 and 0.94 respectively. In their study population VO2peak values were generally 20% lower than age-matched controls without PD tested in the same laboratory (Katzel et al., 2011).

Given the pathophysiology of PD it would be reasonable to assume that aerobic capacity would be lower in individuals with PD than in those without, however the limited number of studies reporting VO2peak in PD have been mixed with some reporting values similar to healthy matched controls (Canning et al., 1997, Protas et al., 1996, Saltin and Landin, 1975, Stanley et al., 1999). Directly comparing all studies is difficult due not only to the study population demographics, but also that some studies used treadmill testing and others a cycle ergometer. Protas et al, identified that aerobic capacity in PD had not been characterised and undertook cycle ergometer and arm-cranking ergometer tests in 8 men with PD (Hoehn and Yahr II-III) and 7 controls. They reported no difference between the groups for VO2peak, and in both groups VO2peak was lower for the arm-cranking test when compared to the lower extremity test. Interestingly they commented that peakVO2 values for both groups were comparable to maximal published values for cycle ergometer tests in older men (Protas et al., 1996).

In 1997, Canning et al published exercise results of 16 patients with mild to moderate PD. Thirteen men and 3 women, Hoehn and Yahr I-III, performed an incremental exercise test to peak work capacity on an electronically braked cycle ergometer. Similar to the results of Protas et al, they found VO2peak values in subjects with PD were not significantly different to normal values. While sedentary subjects produced lower VO2peak scores than exercising subjects, there was no significant correlation between percent predicted VO2peak and PD disease severity (Canning et al., 1997). When interpreting the results of these studies, the small number of participants has to be acknowledged. In contrast to the findings of Canning et al, an abstract published in 2013, in a larger participant group, reported aerobic capacity in PD was affected by rigidity, gait and posture (Sacheli et al., 2013). However very

little detail was included in the abstract about aerobic capacity and measurements and it would appear the abstract has not further been expanded and published as a paper.

In agreement with the afore mentioned studies, Stanley et al found no significant differences in VO2max between those with PD and healthy controls in their study population. They performed cycle ergometry on 20 individuals with PD and 23 healthy controls. Interestingly however they did report that in comparison of time those with PD were unable to exercise for as long before reaching VO2max which may indicate that those with PD may be less efficient during exercise and thus unable to exercise for as long (Stanley et al., 1999).

With a plethora of evidence focussed on the effect of exercise in PD on outcomes such as cognition, quality of life and gait and balance, there is a distinct paucity of research looking at the effect of exercise interventions on aerobic capacity or VO2peak in PD. Bergen et al 2002, investigated the effect of a 16 week aerobic exercise intervention on aerobic capacity and movement initiation time for PD patients finding peak V02 scores significantly improved post intervention, by 26%, as compared to the control group, but only 4 patients (Hoehn and Yahr 2) completed the intervention (Bergen et al., 2002). Though obviously a very small study, this does suggest that aerobic capacity in PD may benefit from exercise interventions.

While investigating the safety and feasibility of a 3 month progressive treadmill aerobic exercise programme for individuals with PD with gait impairment, 5 individuals underwent pre and post programme graded treadmill exercise testing. The study subjects were a limited group with Hoehn and Yahr stage II or above and presence of gait impairment (dragging a leg, freezing or festination), and no change was found in VO2peak post intervention (Skidmore et al., 2008). Similar to previous studies participant numbers were small. Limitations to this study also include; the dependency of the participant group, gait impairment and the exercise test modality. It should also be noted that a number of falls or near misses were observed.

Shulman et al, compared the effects of 3 types of physical exercise on VO2peak in individuals with PD. A total of 67 participants (Hoehn and Yahr I-III) were recruited and randomised to 3 month interventions of one of; higher intensity treadmill training, lower intensity treadmill training or stretching and resistance exercise programmes. Pre and post intervention VO2peak was

measured via treadmill test. Despite a drop-out rate from the study of 19%, both treadmill exercises improved VO2peak (7-8% increase, $p<0.05$) significantly more than the stretching and resistance exercise group (Shulman et al., 2013). Despite the limitations of this study, it does support the findings by Bergen et al that aerobic exercise interventions can improve cardiorespiratory fitness in individuals with PD.

This comprehensive review of aerobic capacity in PD highlights the paucity of research of baseline aerobic capacity and also the effect of exercise interventions to improve cardiorespiratory fitness in PD. Given the significance of impaired aerobic capacity and the potential benefits of improvement, this area warrants significant further research.

Chapter 3. Methods: Cross-sectional study; the pattern of pulmonary dysfunction in idiopathic Parkinson's disease

This project consisted of 2 distinct studies; a cross-sectional study focusing on the pattern of pulmonary dysfunction in IPD, and a randomised control trial (RCT) evaluating the effect of an exercise intervention on pulmonary function, cardiorespiratory fitness and exercise capacity in idiopathic Parkinson's disease. These studies will be described separately. The studies were funded by an innovation grant from Parkinson's UK and a British Geriatrics Society SpR start-up grant. The Newcastle and North Tyneside 1 Research Ethics Committee reviewed the study application on 8th May 2012. Following minor amendments, ethical approval was granted on 30th May 2012.

3.1 Participant recruitment

Participant recruitment commenced in August 2012. Individuals with IPD were recruited from the Northumbria Healthcare NHS Foundation Trust Parkinson's Service, where over 700 patients are on the Northumbria database (though some of these will not meet the Brain Bank Criteria for IPD, and will have other causes of parkinsonism). The service covers a large geographical, mixed rural and urban area in North-East England. Patients were approached in both medical and specialist nurse clinics, and given verbal information and written information sheets to take away (see appendices 9.1). The target recruitment for the study was 100, larger than any previous studies of pulmonary function in PD. Patients who were willing to participate, fulfilled all inclusion criteria and with an absence of exclusion criteria were recruited to the study and asked to sign a consent form (see appendices 9.2). The study consisted of 2 visits.

3.2 Inclusion criteria

Inclusion criteria for the study were:

- Idiopathic Parkinson's Disease by the UK PD Society Brain Bank Criteria.
- Hoehn and Yahr Stage I-IV.
- Ability to provide written informed consent.
- Aged 18 years or over.

3.3 Exclusion criteria

Exclusion criteria for the study were:

- Other forms of Parkinsonism e.g. drug induced.
- Significant medical conditions which would preclude lung function testing.
- Pregnancy.
- Recent diagnosis of a blood clot, deep vein thrombosis, pulmonary embolism or myocardial infarction.
- Unstable cardiac status, haemoptysis, pneumothorax, thoracic, abdominal or cerebral aneurysm.
- Recent eye, thoracic or abdominal surgery.

3.4 Study journey, assessments, questionnaires and outcome measures

After recruitment participants were booked to attend 2 visits at North Tyneside General Hospital. Visit 1 took place in the Education Centre at North Tyneside General Hospital and Visit 2, approximately 1 week later, in the Pulmonary Function Department at North Tyneside General Hospital, Rake Lane, North Shields, NE29 8NH. Transport was arranged if required and travel expenses were reimbursed. Participants received no payment for participation in the study.

At visit 1, consent was confirmed and an assessment document was completed. The assessment included patient demographics, details of the patient's PD, PD medication, PD symptoms, respiratory symptoms, past medical history (PMH), family history (FH), social history (SH), exercise history and general examination. The Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), the Parkinson's Disease Questionnaire (PDQ-39), SCOPA-SLEEP questionnaire, Hospital Anxiety and Depression Scale (HADS), Montreal Cognitive Assessment (MoCA) and an electrocardiogram (ECG) were completed. Permissions were granted for use of all rating scales. At visit 2, full pulmonary function tests were undertaken, with spirometry, lung volumes (plethysmography), diffusion and respiratory muscle strength tests, Mouth Pressures and Sniff Nasal Inspiratory Pressure (SNIP). Figure 12, below, illustrates the patient journey.

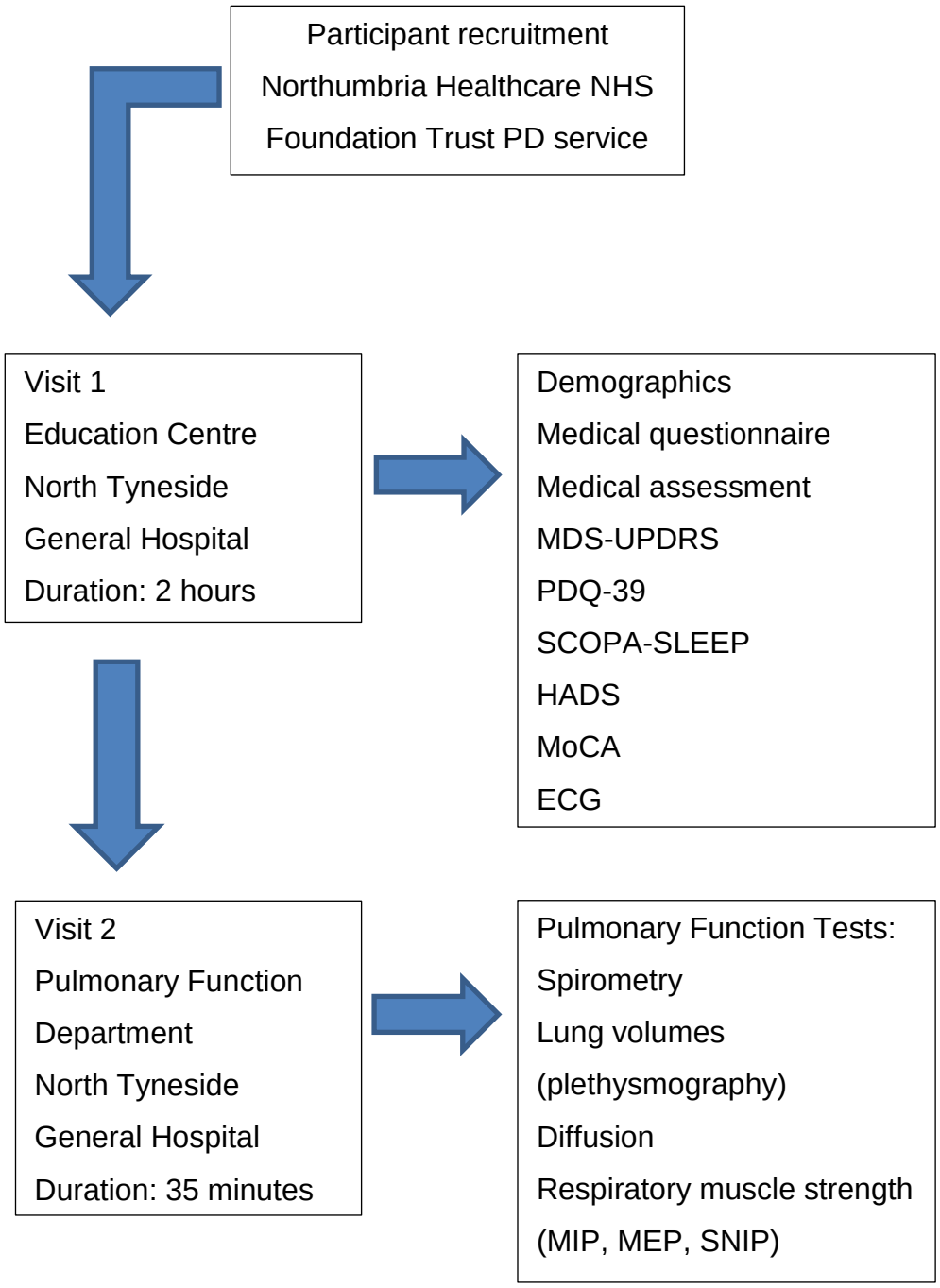

Figure 12: Cross-sectional study patient journey

3.4.1 Assessment document

The assessment document (see appendices 9.3), was created by myself to ensure all relevant information was obtained, particularly focusing on history and examination findings to ensure suitability for safe pulmonary function testing. I undertook the physical examination of all participants. The answers on the assessment document were recorded by one of the Northumbria Healthcare NHS Foundation Trust Parkinson's disease specialist nurses or by myself.

Each participant was allocated a unique identification number and visit number date, age, height and weight were recorded. Details about their PD were obtained; disease duration since diagnosis, symptoms present at onset of PD (bradykinesia, rigidity, tremor, postural instability), laterality of symptoms at onset of PD, current anti-parkinsonian medication, dosage and date commenced and any previous anti-parkinsonian medication used and when discontinued. Accurate medication history was important to identify any individuals who had been exposed to ergot derived dopamine agonists, for example pergolide or cabergoline, due to the potential for these to cause cardiac and pulmonary fibrosis and hence influence pulmonary function test results. Participants were asked about the presence of symptoms that can be associated with PD or PD treatment; hallucinations, REM sleep behaviour disorder, anosmia and history of impulse control disorders. If participants had undergone structural imaging (magnetic resonance imaging (MRI) or computed tomography (CT)) or functional imaging (e.g. DaTSCAN) during their diagnostic work up, the results of these were recorded.

Complete past medical and surgical history was documented and participants were specifically asked regarding any history of cardiovascular disease, stroke, transient ischaemic attacks, peripheral vascular disease, hypertension, dyslipidaemia, diabetes, pulmonary disease, pneumothorax, haemoptysis, joint problems, aneurysms, recent surgery, venous thromboembolism and any chance of current pregnancy. Full medication history and allergy history was documented. Family history was recorded, particularly focussed on parkinsonism, PD, PD plus syndromes, tremor, neurological disorders, stroke, malignancy and cardiac or pulmonary disorders.

Smokers were not excluded from the study, thus not restricting potential numbers of participants, however the results were dichotomised to analyse smokers and non-smokers separately. In view of this, smoking history was careful documented, identifying if individuals were current, ex or never smokers, and pack year history (which can also be calculated for tobacco rather than just cigarette smokers). Social history (SH) was completed by recording of occupations, exposure to pets and alcohol history. Detailed SH was important to identify any factors which may increase risk of pulmonary disease such as exposure to asbestos or birds (which can cause bird fancier’s lung, a type of

hypersensitivity pneumonitis). Exercise history was recorded including weekly frequency, duration and type of exercise.
Finally participants were examined; cardiovascular, respiratory and gastrointestinal systems, blood pressure, pulse and oxygen saturations were recorded, and an ECG was performed.

3.4.2 MDS-UPDRS

The Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) is a validated PD rating scale that is used very commonly in PD research and clinical practice. The MDS sponsored new version of the UPDRS was developed in response to critique of the weaknesses and ambiguities of the original UPDRS. The MDS-UPDRS is divided into four sections; Part I non-motor experiences of daily living, Part II motor experiences of daily living, Part III motor examination and Part IV motor complications. Part III is the only part that is solely completed by the rater, at the end of which an assessment of Hoehn and Yahr stage is made. The Hoehn and Yahr score from 0-V describes the stage of PD objectively rated, where 0 is asymptomatic and V is wheelchair bound or bedridden. Throughout the MDS-UPDRS, higher scores reflect worse signs and symptoms (see appendices 9.4). Use of the MDS-UPDRS also facilitates categorisation of patients into tremor dominant (TD) or postural instability gait difficulty (PIGD) subtypes, based on formulas developed from MDS-UPDRS scores (Stebbins et al., 2013). The MDS-UPDRS raters were either myself or one of the Northumbria Healthcare NHS Foundation Trust Parkinson’s specialist nurses, all of whom are trained in performing the rating scale.

3.4.3 PDQ-39

The Parkinson’s Disease Questionnaire (PDQ-39) is a subjectively completed quality of life questionnaire (Peto et al., 1995). A short form of the questionnaire, the PDQ-8, is also validated for use (Jenkinson et al., 1997). The PDQ-39 provides a summary index score for the entire questionnaire and separate scores across 8 domains or scales; mobility, activities of daily living (ADL), emotional well-being, stigma, social support, cognitions, communication and bodily discomfort (see appendices 9.4). In similarity to the MDS-UPDRS, higher scores reflect worse symptoms. The PDQ-39 was selected for use in this study for a number of reasons; it is validated; it is a MDS recommended scale for use

in PD; it is very commonly used in PD research thus allowing comparisons; it is comprehensive and data exists on sensitivity to change of the PDQ-39 and minimally important difference.

3.4.4 SCOPA-SLEEP

The SCOPA-SLEEP scale is a valid and reliable scale to quantify sleep issues in PD. The SCOPA–SLEEP consists of two sections (night –time sleep problems and daytime sleepiness) and an additional 7-point question as a global measure of night time sleep quality. The night-time sleep problems subscale includes; sleep initiation, duration, fragmentation, efficiency and early wakening. The daytime sleepiness subscale includes frequency of falling asleep unexpectedly in particular situations, having difficulty staying awake and daytime sleepiness. As previously, higher scores reflect worse symptoms (Marinus et al., 2003). The SCOPA-SLEEP scale was selected for use in this study over other sleep scales due to it assessing both nocturnal sleep disorders and daytime somnolence to a similar extent. For example the Parkinson's Disease Sleep Scale (PDSS) can be used to obtain a profile about potential causes of bad sleep, but is barely useful in the assessment of daytime sleepiness (Martinez-Martin et al., 2008). The SCOPA-SLEEP is a subjectively completed rating scale which is recommended by the MDS (see appendices 9.4).

3.4.5 HADS

Although prevalence rates of anxiety and depression in PD vary across studies, it is widely acknowledged that rates are substantial (Pontone et al., 2009, Reijnders et al., 2008). No PD specific rating scales of anxiety and depression are commonly used. The Hospital Anxiety and Depression Scale (HADS) is a 14 item scale - 7 items relate to anxiety and 7 to depression. This outcome measure was specifically developed to differentiate anxiety and depression from common somatic symptoms of illness, for example fatigue or insomnia, thus creating a tool for the detection of anxiety and depression in individuals with physical health problems. Each item on the questionnaire is scored from 0-3, thus a person can score up to 21 for either anxiety or depression (Snaith and Zigmond, 2000). A systematic review of a large number of studies concluded a cut-off point of 8/21 for diagnosis of anxiety or depression (Bjelland et al., 2002).

The HADS is a MDS recommended rating scale for use in individuals with PD (see appendices 9.4).

3.5 Pulmonary function measurement

Participants attended the Pulmonary Function Department at North Tyneside General Hospital. All testing was performed by qualified, experienced respiratory physiologists accredited to the Association for Respiratory Technology and Physiology (ARTP). The ARTP are the professional guardians of physiological measurement in respiratory medicine in the UK and provide the only national, professionally recognised, qualifications in respiratory function testing and spirometry. They achieve this through standards of training and quality assurance (ARTP, 2017). The variability in lung function measurements can be very high, unless high-quality measurements, expertly trained staff and high-quality assurance processes are in place, thus the decision to perform all testing with respiratory physiologists to ensure gold standard testing. All equipment used was regularly calibrated according to guidelines.

Before testing commenced all patients had height and weight recorded, to enable calculation of Body Mass Index (BMI). If standing height could not be measured easily, for example due to severe kyphoscoliosis, arm span was measured instead, which is normal practice in these circumstances. Smoking history and use of inhalers the same day was also documented.

When performing PFTs, dynamic studies (spirometry, flow volume loops, peak expiratory flow rates) are performed first followed by lung volumes and diffusion capacity (Ranu et al., 2011). Respiratory muscle strength testing is performed subsequently. Interpretation of PFTs is based on comparisons of data with reference (predicted) values. The European Community for Coal and Steel (ECCS) have published comprehensive listings of reference equations which were used in this study (Quanjer et al., 1993). Medisoft's BodyBox 5500 was used for measurement of spirometry, lung volumes and diffusion. Micro Medical's MicroRPM^{TM} respiratory pressure meter was used for respiratory muscle strength testing. In association with the BodyBox 5500, the computer software used was Medisoft Expair 2010, 1.29, 13. All equipment met the specification standards of the ATS and ERS.

All procedures were explained before and during the testing and encouragement during testing is important to achieve optimal accurate results.

Test procedures followed the recommendations of the BTS and the ARTP publication on guidelines for the measurement or respiratory function (ARTP/BTS, 1994).

3.5.1 Spirometry

Participants were tested in an upright sitting position and wearing a nose clip. The spirometer was fitted with a bacterial filter. The participant then sealed their mouth around the mouthpiece of the spirometer and breathed in and out normally for the measurement of tidal volumes (TV). Relaxed or slow vital capacity (VC) was measured next; the patient was instructed to breathe in as deeply as possible (to full inspiration), seal the lips tightly around the mouthpiece and then breathe out into the spirometer at a sustained, comfortable speed to full expiration. For VC the best result was recorded from a maximum of 4 tests.

Forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) and flow volume curves were measured next. The equipment was able to measure the maximal flow volume curve, FEV1, FVC and PEF using the same expiratory manoeuvre, however to facilitate reader understanding of the technique I shall describe these separately starting with FEV1 and FVC measurement. The participant was instructed to breathe in to maximal inspiration then form a tight seal with the lips around the spirometer mouthpiece and breathe out as hard and fast as possible until no further air could be exhaled. A maximum of 8 tests were done to achieve 3 reproducible tests. Three valid, or technically acceptable tests, should have FEV1 and FVC highest values within 5% or 100mls. The highest FEV1 and FVC, which did not have to come from the same test, were selected for reporting. Potential sources of errors which would lead to a test being rejected included; leak at the mouth, not inspiring to TLC, tongue or false teeth obstructing mouthpiece, poorly coordinated start to the manoeuvre, coughing and sub-maximal effort (ARTP, 2003).

Peak expiratory flow (PEF) was measured as part of the forced expiratory manoeuvre used to measure FEV1 and FVC, and the highest value which correlated with the highest FEV1 was recorded. The maximal flow volume curves measurement technique is largely to similar to that described above. A nose clip is essential and the participant was asked to breathe in to full inspiration and then seal lips tightly around the mouth piece and blow out as

hard and fast as possible until the lungs were empty and then breathe in as hard and fast as possible until the lungs were completely full again. Criteria for test acceptability was as for FEV1 and FVC testing, and the flow volume curve was visibly displayed for inspection. Values for maximum expiratory flow (MEF) and maximum inspiratory flow (MIF) were recorded from these curves.

3.5.2 Lung volumes

Lung volumes were measured using whole body plethysmography in a constant volume box. This technique, discussed in section 2.3.4, was described by Dubois et al, and later reviewed in an ERS/ATS workshop series (Dubois et al., 1956, Coates et al., 1997). Boyle's law (pressure x volume = constant) is the fundamental basis for its operation (ARTP, 2003). The patient was enclosed in an airtight box, the door was shut and temperature and pressure were allowed to stabilise. A pneumotachograph at the mouth allowed measurement of airflow and a shutter was used to occlude the airway during the testing when required. Pressure was measured in the box and at the mouth by pressure transducers. When respiratory efforts continue and the mouthpiece is occluded, changes in the box pressure reflect rarefaction and compression of gas within the thorax and can be used to calculate thoracic gas volume (TGV) (ARTP, 2003).

The procedure was clearly explained as breathing against a closed shutter can be an unusual feeling for patients. With a nose clip insitu, the patient was attached to the mouthpiece and was asked to breathe normally. The shutter was closed at the end of a tidal expiration and the patient was asked to pant/breathe gently against the shutter (approximately 1 breath per second). The shutter was reopened and the patient was asked to breathe fully in to maximal inspiration and then fully out (relaxed or slow VC). This recorded inspiratory vital capacity (IVC) and expiratory reserve volume (ERV). The computer software then applied a line of best fit for calculation of total lung capacity (TLC) and residual volume (RV). The procedure was repeated to ensure reproducibility and when this was achieved, with 2 functional residual capacity (FRC) recordings within a 5% match, the mean of the 2 was calculated and recorded.

Unlike other lung function tests, there is no maximum number criteria for attempts as lung volume measurement is less effort dependent. Individuals with

severe airflow limitation may tire however. Due to the technique, sources of error with whole body plethysmography are very few (ARTP, 2003).

3.5.3 Diffusion

The gas exchange characteristics of the lungs were assessed by measuring Transfer factor for carbon monoxide (TLCO), by the single breath breath-hold technique. This has to be done after measurement of VC as this figure is required for the procedure. The apparatus consisted of an industrial gases cylinder with the gas mix in, an inspiratory start bag and a bag to collect the expired sample. The cylinder (BOC) contents at the start of the test were carbon monoxide (CO) 0.28%, helium (He) 14%, oxygen (O_2) 18% and nitrogen balance. The inspiratory start bag (1.8L) was filled with the test gas and composition analysed by the machine. Volumes could be reduced in patients with small lung volumes.

With a nose clip insitu, the patient was connected to the system via a mouthpiece. The patient was instructed from RV (having breathed out as far as possible), to take a sharp breath in and maximally inhale as far as possible. For a valid reading the patient had to inspire >85% of VC. The patient was then asked to breath hold for 10 seconds (should not be less than 6 seconds) and then breathe out slowly, as far as possible, to maximal expiration into the expired sample bag. Of note it is more important to inspire >85% VC than breath hold for 10 seconds for valid results. During the exhalation, the initial portion (washout) from the anatomical and instrument deadspace was discarded to ensure that sample is representative of alveolar gas (ARTP, 2003). The gas concentrations in the expired bag were then analysed and compared to the inspired bag to calculate TLCO and hence gas exchange characteristics.

A maximum of 5 attempts (due to carbon monoxide) were performed, with the aim to produce 2 reproducible TLCO results within 5% of each other. At least 4 minutes was left between attempts. The recorded results were a mean of the 2 best results. If TLCO was not reproducible within 5%, the best was recorded and a comment made. Diffusion results were reported for assumed haemoglobins and correction equations were done for those participants with documented recent haemoglobin results.

3.6 Respiratory muscle strength

Respiratory muscle strength was measured using a hand-held respiratory pressure meter, the Micro Medical MicroRPM^{TM}. The MicroRPM was used to measure the maximal expiratory pressure at the mouth (MEP), the maximal inspiratory pressure at the mouth (MIP) and the sniff nasal inspiratory pressure (SNIP). There was no set amount of maximal tests and the tests were repeated until 3 were reproducible within 10%. The best result was recorded. Nose clips are not used during respiratory muscle strength testing.

To assess MEP, the expiratory valve, the bacterial filter and the rubber mouthpiece were attached. The meter was put in “MIP/MEP” function. The patient was requested to inhale maximally (to TLC), put the mouthpiece with the bite blocks between the teeth and the lips over the flange and then blow out as hard as possible.

To assess MIP, the inspiratory valve, the bacterial filter and the rubber mouthpiece were attached. The meter was put in “MIP/MEP” function. The patient was instructed to exhale maximally, until the lungs felt empty (RV), and with mouthpiece as before, then take a fast, as hard as possible, breath in.

To assess SNIP, the nasal plug adaptor and appropriately sized nasal probe were attached to the MicroRPM. The meter was put in “SNIP” mode. The nasal probe was inserted into one nostril, with the patient supporting the probe. At the end of a normal breathing cycle, the patient was asked to perform a short sharp sniff with as much effort as possible. The other nostril was not occluded during the procedure. Each nostril was tried once and then the nostril that achieved the highest result was repeatedly used until 3 results were reproducible within 10%.

Results for MIP and MEP reflect the highest value maintained over 1 second, as opposed to SNIP which records the highest value.

Respiratory muscle strength testing concluded the pulmonary function tests.

Chapter 4. Results, Discussions and Conclusions: Cross-sectional study; The pattern of pulmonary dysfunction in idiopathic Parkinson's disease

With the distinction between the 2 sections of the study, this chapter concerns the results, discussion and conclusion of the cross-sectional study. Having been approached by the Northumbria PD team, 103 patients volunteered to take part in the study.

Three participants failed to complete the study, by inability to attend visit 2. Two participants completed visit 1 and due to time pressures and other commitments were unable to attend visit 2. The other participant, during visit 1, gave a history consistent with pulmonary embolism and was admitted to hospital for investigations and excluded from visit 2. Thus of the 3 who discontinued the study, 2 were withdrawals by the participants and 1 had participation terminated by the investigator. Figure 13, below, summarises the recruitment, drop out and completion.

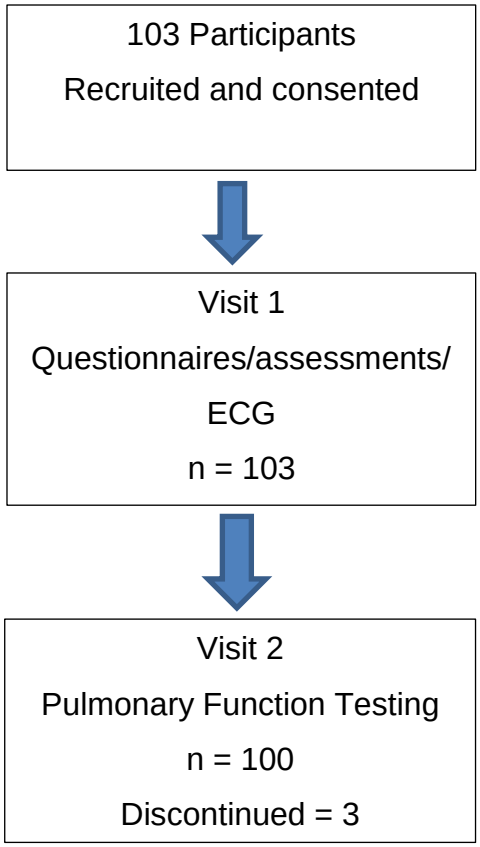

Figure 13: Cross-sectional study recruitment, drop-out and completion

Results were inputted by a research assistant and second checked by myself. Only very few data points were missing from the entire dataset of the cross-sectional study (3 participants had some answers missing from the PDQ-39, 2 had answers missing from the HADS and 1 had answers missing from the SCOPA-SLEEP). As a consequence no attempt was made to impute the missing values and the data are presented as collected. Where data are missing they have been listed. As such missing data have been assumed to be missing completely at random and so non-informative. The data from both groups were not normally distributed, on review of histograms, as such medians and interquartile ranges are quoted and non-parametric tests (Mann-Whitney U tests) were used to analyse the unpaired data. Visual inspection of the data distribution using histograms was used for assessing normality. The statistical normality tests are auxiliary to the graphical assessment. Statistical tests have the advantage of making an objective normality assessment, but are disadvantaged by sometimes lacking sensitivity at low sample sizes (having little power to reject the null hypothesis and thus passing normality tests) or being overly sensitive to large sample sizes (significant results derived even in the case of a small deviation from normality) (Ghasemi and Zahediasl, 2012). In cases where there was any discrepancy in the distribution on visual inspection, the statistical Kolmogorov-Smirnov test of normality was used. For categorical data, e.g. male or female, Chi-square test was used. Alpha was set at 0.05.

4.1 Demographic features

Smokers and those with known obstructive lung disease, for example asthma or COPD, were not excluded from the study. However the results were dichotomised and analysed as 2 separate groups. One group was termed “smokers” and included any individual with a known history of obstructive lung disease and those who had a 10 pack year or greater smoking history. The other group were termed “non-smokers” and included any participant without known lung disease, lifelong non-smokers and those with a smoking history of less than 10 pack years. The term “pack year” is a widely used quantification of a person’s smoking history to measure tobacco exposure. One pack year is equivalent to smoking 20 cigarettes per day for 1 year, thus if an individual smoked 40 cigarettes a day for 10 years they would have a 20 pack year smoking history.

The results were dichotomised to avoid any false positive results as the prevalence of obstructive pulmonary function test results would be expected to be higher in the “smokers”. Table 4, below, illustrates a comparison of the basic demographics between the 2 groups (non-smokers and smokers). There were 64 in the non-smokers group and 36 in the smokers group. The smokers and those with known obstructive lung disease group comprised 20 smokers with a history of 10 or more pack years (but without a known diagnosis of obstructive lung disease), 13 with a diagnosis of asthma and 3 with a diagnosis of COPD. The 3 with COPD all had pack year histories over 10 years. Of the 13 with a past medical history of asthma, 3 had pack year histories over 10 years also, 3 had smoking histories of less than 10 years and 3 were not prescribed any inhalers at all. The participants were asked if they had ever been given a diagnosis of asthma but were not asked how the diagnosis was made, thus it has to be remembered that there is a possibility of historically incorrect diagnoses of asthma particularly if spirometry with reversibility testing has not been accurately performed by trained individuals. Thus 26 of the 36 in the smokers group had a smoking history of 10 or more pack years.

Particularly in a research setting it is difficult to interpret results and make comparisons when patients are on a number of different medications and at different doses. To address this issue, Tomlinson et al calculated conversion factors for different antiparkinsonian drugs to give a total daily levodopa equivalent dose (LED). They undertook a systematic review of studies identifying 56 primary reports of LED estimates, extracted data, calculated modal and mean LEDs and derived a standardised LED for each antiparkinsonian drug. The conversion factor for each drug was to have the same antiparkinsonian effect as 100mg of levodopa. Thus for immediate release levodopa the conversion factor was x1, controlled release levodopa x0.75, Duodopa x1.11, Pramipexole (as salt) x100, Ropinirole x20, Rotigotine x30, Selegiline (oral) x10, Rasagiline x100, Amantadine x1, Apomorphine x10 and Entacapone was levodopa x0.33 (Tomlinson et al., 2010). This formula was used to calculate LEDs in this study making it comparable to other large studies including PD MED and PD SURG.

	Non-smokers N=64 Median (IQR)	Smokers N=36 Median (IQR)	Significance
Age (years)	68.0 (63.0 – 76.8)	71.5 (66.0 – 76.8)	Z = -0.755 P = 0.450
Male (%)	N = 44 (68.8%)	N = 27 (75.00%)	 P = 0.509
BMI (kg/m^2)	26.6 (23.9 – 30.0)	28.2 (24.9 – 32.0)	Z = -1.339 P = 0.180
Disease duration (months)	48.0 (21.0 – 83.8)	52.0 (14.3 - 108.0)	Z = -0.305 P = 0.760
Levodopa equivalent dose (mg)	490.0 (270.0 – 655.0)	500.0 (300.0 – 862.3)	Z = -0.640 P = 0.522

Table 4: Comparison of the basic demographics between non-smokers and smokers

(Significance tests Mann-Whitney U in all except Male. Male Chi-square test.)

No statistically significant difference was observed between the non-smokers and smokers with respect to age, sex, BMI, disease duration and levodopa equivalent dose.

4.2 UPDRS Results

The results of the four sections of the MDS-UPDRS (Part I non-motor experiences of daily living, Part II motor experiences of daily living, Part III motor examination and Part IV motor complications) are reported in table 5, below, comparing smokers to non-smokers. Part III is the only part that is solely objective and completed by the rater. Table 5 also illustrates the Hoehn and Yahr scores and motor phenotype as derived from the MDS-UPDRS using widely adopted formulas (Stebbins et al., 2013). Motor phenotype is reported as tremor dominant (TD), postural instability gait difficulty (PIGD) subtype or indeterminate. As for the demographics, the data from both groups were not normally distributed and as such medians and interquartile ranges are quoted and non-parametric tests (Mann-Whitney U tests) were used to analyse the

unpaired data. For categorical data Chi-square test was used. Alpha was set at 0.05.

No statistically significant difference was seen between the groups in the objectively assessed UPDRS part 3 scores, however a statistically significant difference was seen between the groups for the subjectively assessed UPDRS part 1 and 2 scores. Median Hoehn and Yahr score was the same in both groups. Figures 14 and 15, below, illustrate the derived motor phenotypes in each group. The smokers group had a statistically significant higher percentage of individuals with PIGD motor phenotype.

	Non smokers N=64 Median (IQR)	Smokers N=36 Median (IQR)	Significance
UPDRS Part 1	7.0 (4.0 – 13.0)	11.0 (9.0 – 15.5)	Z = -3.206 P = 0.001
UPDRS Part 2	9.0 (5.3 – 15.0)	13.5 (9.3 – 19.0)	Z = -2.809 P = 0.005
UPDRS Part 3	27.5 (20.0 – 35.0)	25.5 (20.0 – 41.5)	Z = -0.765 P = 0.444
UPDRS Part 4	0.0 (0.0 – 3.0)	0.0 (0.0 – 3.0)	Z = -0.300 P = 0.764
Hoehn and Yahr	2.0 (2.0 – 2.0)	2.0 (2.0 – 3.0)	Z = -1.292 P = 0.196
Motor phenotype PIGD (%)	N = 37 (57.8%)	N = 28 (77.8%)	P = 0.045
Motor phenotype TD (%)	N = 21 (32.8%)	N = 6 (16.7%)	P = 0.081
Motor phenotype Indeterminate (%)	N = 6 (9.4%)	N = 2 (5.6%)	P = 0.499

Table 5: Comparison of UPDRS, Hoehn and Yahr and motor phenotype between non-smokers and smokers

(Significance tests Mann-Whitney U in all except Motor phenotype. Motor phenotype Chi-square test.)

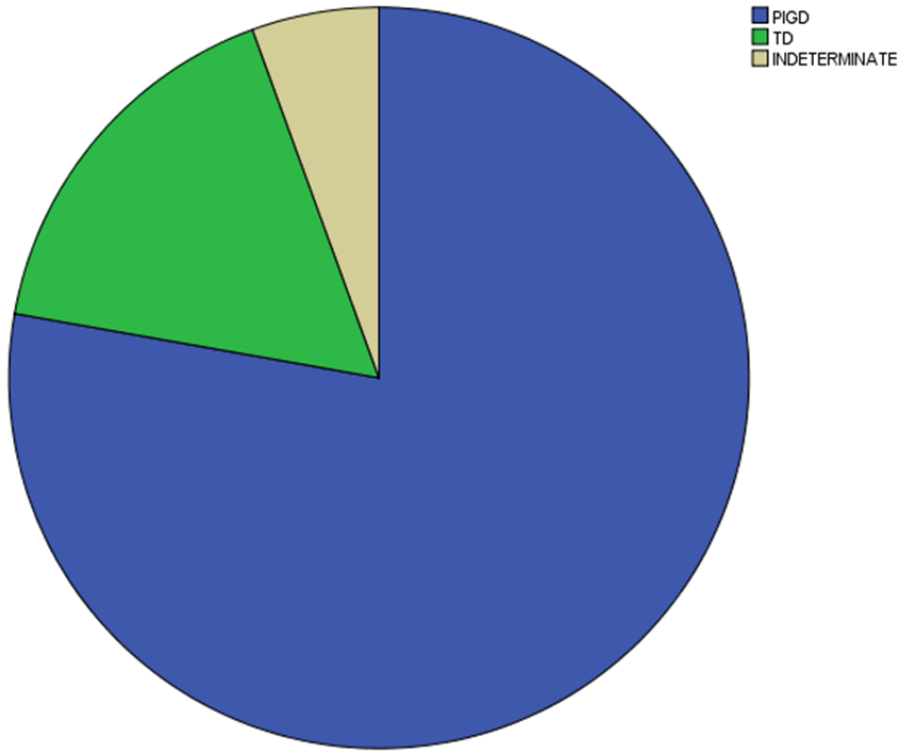

Figure 14: Motor phenotype of smokers group

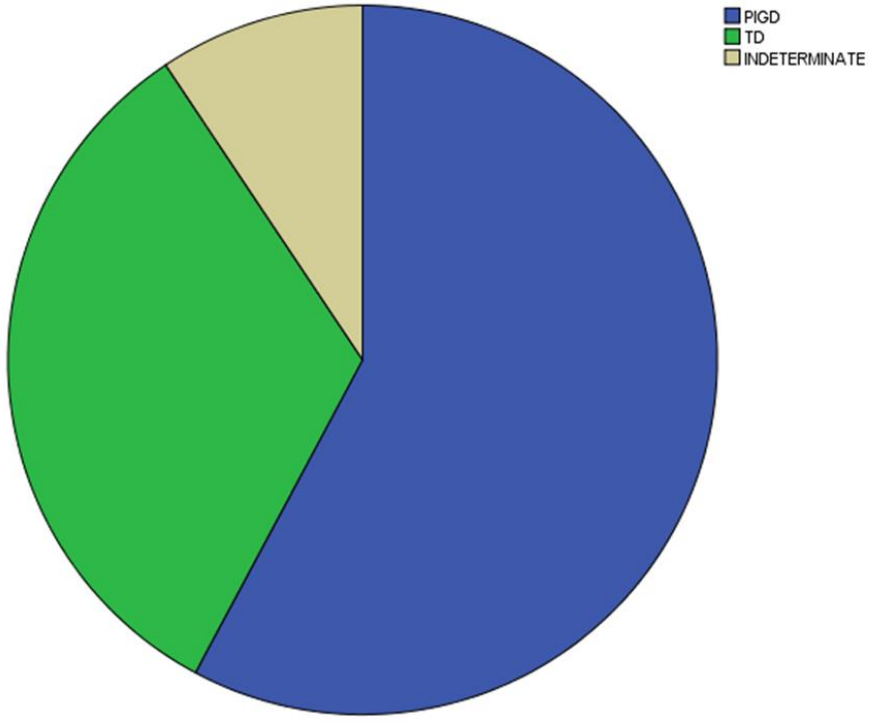

Figure 15: Motor phenotype of non-smokers group

4.2.1 Discussion

The demographic, UPDRS and motor phenotype data, compared between non-smokers and smokers, yielded interesting results. While the groups were comparable with no significant difference between the groups on age, sex, BMI, disease duration and levodopa equivalent dose, differences were apparent in UPDRS scores and motor phenotype. The objective UPDRS section 3 scores were not significantly different between the 2 groups, with the non-smokers median score being 2 points higher than the smokers indicating a trend towards the non-smokers having worse motor scores. Similarly there was no difference in the objective Hoehn and Yahr scores between the groups. However the subjective UPDRS part 1 and 2 scores were significantly different between the groups with the smoker's median scores being significantly higher than the non-smokers indicating that the smokers rated themselves worse for non-motor and motor experiences of daily living.

There are a number of potential reasons for these findings. One of the symptoms of lung disease is shortness of breath on exertion and this may limit an individual's ability and increase the time it takes to perform tasks. Section 3 of the UPDRS does not require significant physical exertion by the patient where as some of the subjective assessments of sections 1 and 2, including eating, dressing, hobbies, walking and getting out of bed, a car or a deep chair require more physical exertion and may thus be scored higher with individuals with lung disease. Lung disease may also impact on fatigue and sleep leading to higher subjective ratings on these questions in UPDRS sections 1 and 2. Thus an individual may appear objectively better on short, non-exertional assessments. UPDRS sections 1 and 2 also include questions pertaining to anxiety and depression which may also be affected by lung disease but also may be affected by smoking in the absence of lung disease (Munafo and Araya, 2010, Moussavi et al., 2007). Anxiety and depression and their impacts on perception of health and abilities are important considerations also.

Focussing on motor phenotype there was a statistically significantly higher prevalence of PIGD phenotype in the smokers group, and although it did not reach statistical significance there was a higher prevalence of TD phenotype in the non-smokers group. Remembering this group included both smokers and those without a smoking history but with a diagnosis of obstructive lung disease, these are interesting findings. Smoking and PD has long been of interest,

particularly in the research setting, dating back nearly half a century, prospective and retrospective studies have demonstrated an inverse correlation between PD and smoking concluding a reduced risk of developing PD in smokers and a recent large study concluded smoking duration was more associated with lower PD risk than smoking intensity (Baumann et al., 1980, Marttila and Rinne, 1980, Checkoway et al., 2002, Chen et al., 2010). Thus considering smokers alone, do one or more of the 600 ingredients in cigarettes, creating more than 7000 chemicals when burnt, have cellular influences that affect the expressed phenotype of PD to give a higher prevalence of the PIGD phenotype? This question remains unanswered in current published research. Depression, apathy and hallucinations are more prominent in the PIGD phenotype which may have contributed to the UPDRS part 1 and 2 scores being higher in the smokers group (Reijnders et al., 2009). The PIGD phenotype usually presents a more severe pattern of non-motor features, faster motor deterioration, faster rate of cognitive decline and is associated with progression of disability and a negative impact on survival (Burn et al., 2006, Post et al., 2007, Auyeung et al., 2012, Poletti et al., 2012, Vu et al., 2012, Moustafa and Poletti, 2013). With these facts in mind, considering the patients included in the smokers group that do not have a smoking history but have a historical diagnosis of obstructive lung disease caused by asthma, the question arises about the potential of a misdiagnosis of asthma. It is a feasible suggestion that their obstructive spirometry could be caused by PD rather than asthma and given the pathophysiology would be more likely to be present in the PIGD than TD phenotype. Including these participants in the smokers group may give the impression of a higher prevalence of PIGD in this group. This theory is further discussed with the pulmonary function results.

4.3 PDQ-39, SCOPA-SLEEP, HADS Results

The results of the patient reported questionnaires are reported in table 6, below. The Parkinson's Disease Questionnaire (PDQ-39), subjectively completed quality of life questionnaire, summary index score for the entire questionnaire is quoted. The SCOPA-SLEEP scale to quantify sleep issues is described as SCOPA B (sleep at night), SCOPA C (global measure of night time sleep quality) and SCOPA D (sleep during the day and evening). The Hospital Anxiety and Depression Scale (HADS) is separately documented as HADS A (anxiety)

and HADS D (depression). For all 3 rating scales (PDQ-39, HADS and SCOPA-SLEEP) higher scores reflect worse symptoms.

	Non smokers N=64 Median (IQR)	Smokers N=36 Median (IQR)	Significance
PDQ 39 summary index	12.7 (7.1 – 29.3)	23.1 (14.3 – 36.4)	Z = -2.573 P = 0.010
SCOPA B	4.0 (2.0 – 7.0)	5.0 (1.0 – 8.0)	Z = -0.195 P = 0.846
SCOPA C	3.0 (2.0 – 4.0)	3.0 (1.0 – 4.0)	Z = -0.067 P = 0.946
SCOPA D	3.5 (2.0 – 5.8)	4.0 (3.0 – 6.8)	Z = -1.504 P = 0.133
HADS A	4.0 (2.0 – 6.3)	3.5 (2.0 – 8.8)	Z = -0.645 P = 0.519
HADS D	3.0 (2.0 – 6.0)	7.0 (3.0 – 8.0)	Z = -2.765 P = 0.006

Table 6: Comparison of PDQ-39 summary index, SCOPA-SLEEP and HADS between non-smokers and smokers

(Significance tests Mann-Whitney U.)

Statistically significant differences between the groups were observed in quality of life, as reported by the PDQ-39 summary index, and in depression, as reported by the HADS. These results indicated worse symptoms in the smokers group.

4.3.1 Discussion

The self-reported questionnaires; PDQ-39, SCOPA-SLEEP and HADS reflecting quality of life, day time sleepiness, night time sleep quality and anxiety and depression provided very interesting results. There was a trend for the smokers group (including those with known obstructive lung disease history), to rate themselves worse for quality of life, sleeping during the night, sleeping during the day and evening, and depression. The only subjective outcome where the smokers group rated themselves better than the non-smokers was anxiety. Statistically significant differences between the 2 groups were in the

PDQ-39 summary index and in the depression scores, with the smokers reporting significantly worse symptoms reflected by higher scores. There was a large difference in the median PDQ-39 scores between the 2 groups with the smokers' median of 23.1 and the non-smokers' median of 12.7. These scores mirror the subjective UPDRS part 1 and 2 scores, reported in section 4.2, with the smokers' median scores being significantly higher than the non-smokers. However it must be remembered that the objectively assessed UPDRS part 3 scores (see section 4.2) and Hoehn and Yahr scores were not significantly different between the 2 groups. Thus despite no objective difference in motor scores and PD disease severity, the smokers reported worse quality of life and higher depression scores.

The PDQ-39 asks participants questions with the prefix "due to having Parkinson's disease, how often in the last month have you……" with a variety of questions to follow such as "had difficulty walking half a mile?". A large number of the questions require significant activity such as; had difficulty with leisure activities, looking after your home, difficulty washing and dressing or have you been confined to the house. Smokers or those with lung disease may suffer symptoms such as breathlessness on exertion that limit their activities and although the questionnaire asks the effect of having PD on their activities, it is feasible that individuals may have answered describing the effect of respiratory symptoms on their activities in addition to their PD symptoms resulting in higher scores in the smoker's group. With the breadth of potential PD symptoms, it can be difficult for both patients and clinicians to ascertain which symptoms are attributable to PD and which are caused by other conditions. There is significant crossover of questions in the PDQ-39 and the HADS, with the PDQ-39 enquiring about feelings of being frightened, worried, angry, bitter, depressed, isolated, lonely, weepy, tearful and anxious. Thus using the PDQ-39 summary index score, which includes all domains, those individuals with higher anxiety and depression (particularly depression) scores will record worse quality of life scores reflected in higher PDQ-39 scores.

The smokers group includes those with a known diagnosis of a chronic obstructive lung disease and those with a significant smoking history. Thus there are two distinct areas to consider within this group; the effect of chronic respiratory disease on quality of life, anxiety, depression and sleep and separately the effect of smoking on these outcomes. Quality of life is a

multifaceted, complex concept and most studies in individuals with chronic diseases refer to health related quality of life (Megari, 2013). The World Health Organization defines quality of life as “an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” (WHOQOLGroup, 1993). Health related quality of life is multidimensional and comprises at least three broad domains, physical, psychological and social functioning, that are affected by an individual’s disease and/or treatment (Sprangers, 2002). As individuals are living longer and the management of chronic diseases improves, the prevalence of those living with a chronic disease that can adversely affect their quality of life has increased. Although there are cultural differences in results, depression is frequently found to have a greater impact on health related quality of life than other chronic diseases (Megari, 2013). If individuals have the comorbid state of depression this incrementally worsens health compared with depression alone, with another chronic disease alone and with combinations of chronic diseases without depression (Moussavi et al., 2007). Both Asthma and COPD are known to have a negative impact on quality of life and this further deteriorates with increasing disease severity (Stahl et al., 2005, Gonzalez-Barcala et al., 2012). Anxiety and depression are particularly common in patients with COPD. Whilst the prevalence varies considerably among studies it is probably higher than is currently reported. Significant symptoms of depression have been reported in up to 74% of those with COPD (Rubio et al., 2009, Yellowlees et al., 1987, Karajgi et al., 1990, Light et al., 1985, Yohannes et al., 2000). Similarly to COPD, asthma is associated with increased prevalence of anxiety and depression and the presence of an anxiety or depression is highly associated with increased asthma symptom burden (Moussas et al., 2008, Richardson et al., 2006). With 16 of the 36 participants in the smokers group having a diagnosis of COPD or asthma it is likely that their chronic respiratory disease contributed to the higher and thus significantly worse scores for quality of life as assessed by the PDQ-39 and depression as rated by the HADS.

The causal direction between smoking and anxiety and depression remains a debated one and for obvious ethical reasons, randomised control trials cannot be conducted to unequivocally answer this question. Smokers often describe the anxiolytic and antidepressant effects of smoking, but evidence exists to

suggest that smoking may increase negative affect suggesting the association is in the opposite direction and that smoking leads to depression (Boden et al., 2010, Munafo and Araya, 2010). Many questions remain; does depression cause people to smoke to self-medicate symptoms? Does smoking cause increased depression risk via neurotransmitter pathway alterations in chronic exposure? Is the relationship bidirectional in that acute or infrequent smoking reduces negative affect, but chronic smoking exacerbates it (Munafo and Araya, 2010)? Depression and lower quality of life are associated with higher probabilities of smoking initiation and lower likelihoods of successful cessation of smoking. There is a negative relationship between smoking and quality of life, with the degree related to the number of cigarettes smoked. Interestingly passive smoking is also negatively associated with quality of life, whilst cessation of smoking improves quality of life (Goldenberg et al., 2014). Whichever the direction of the causal association, with 26 out of 36 in the smokers group having a significant smoking history, this provides an explanation to the observed statistically significantly worse subjective assessments of quality of life and depression in the smokers group.

4.4 Pulmonary Function Results

The pulmonary function testing provided both quantitative and qualitative results for each participant. The pulmonary function and respiratory muscle strength tests reported in excess of 25 variables for each participant thus appropriate selection of quantitative variables is vital to ensure the results can be easily interpreted and compared to previous studies. The flow volume loops also provided visual qualitative information pertaining to upper airway obstruction. Initially the PFT results were reviewed to ascertain in the lung function is normal, if there is evidence of airflow obstruction or if there is any evidence of restriction. The PFT data from both groups (smokers and non-smokers) were not normally distributed, on review of histograms, as such medians and interquartile ranges are quoted where appropriate. Visual inspection of the data distribution using histograms was used for assessing normality, as in chapter 4 in cases where there was any discrepancy in the distribution on visual inspection the statistical Kolmogorov-Smirnov test of normality was used. Focusing first on the spirometry, lung volumes and flow volume loop results, the results are best displayed in 2 ways; with median and interquartile ranges and

also the number of individuals with a particular pattern of lung dysfunction. All 100 participants were able to perform technically acceptable spirometry and all but 3 were able to perform the assessments of lung volume. Of the 3 that were unable to produce results for lung volume, 2 were from the non-smokers group and 1 from the smokers group. The reasons for inability to complete the lung volume assessments in the 2 participants in the non-smokers group were; 1 was unable to comply fully with the instructions given and 1 was too dyskinetic to be able to technically measure accurately to an acceptable level. In the smokers group, the individual who failed to complete the lung volume assessments was too claustrophobic to allow the body plethysmography box door to be shut thus precluding lung volume measurement in this way. We considered the use of helium dilution as an alternative to body plethysmography in this participant however concluded that it was preferable to report all results measured in the same way. Table 7 below, illustrates the median and interquartile ranges of a number of spirometry and lung volume variables.

	Non smokers N=64 Median (IQR)	Smokers N=36 Median (IQR)
FEV1 % PREDICTED (%)	108.00 (94.00 – 115.25)	107.00 (88.00 – 118.00)
FVC % PREDICTED (%)	113.50 (101.75 – 125.75)	122.00 (95.75 – 130.00)
VC % PREDICTED (%)	109.50 (97.75 – 123.00)	116.50 (98.00 – 131.25)
FEV1/FVC OBSERVED (%)	74.92 (69.20 – 77.57)	69.53 (63.49 – 76.07)
FEV1/VC OBSERVED (%)	74.96 (69.73 – 76.93)	68.19 (63.01 – 74.03)
FEF25-75 % PREDICTED (%)	83.50 (60.25 – 100.50)	61.50 (34.75 – 83.00)
PEF % PREDICTED (%)	100.50 (84.00 – 111.25)	97.50 (82.00 – 110.25)
RV % PREDICTED (%)	121.50 (100.00 – 141.75)	126.00 (113.00 – 147.50)
TLC % PREDICTED	107.50 (98.00 – 119.75)	113.00 (103.50 – 121.00)
RV/TLC OBSERVED (%)	43.95 (37.34 – 48.55)	44.46 (39.87 – 50.04)

Table 7: Comparison of group median results of spirometry and lung volumes between non-smokers and smokers

As illustrated in the table above, in both the non-smokers and smokers groups the FEV1 % predicted, FVC % predicted and VC % predicted medians were all above 100%. The FVC % predicted and the VC % predicted medians were higher in the smokers than in the non-smokers group. The FEV1/FVC observed and FEV1/VC observed medians were above 70% in the non-smokers group and below 70% in the smokers group. The median results indicated obstruction in the smokers group. VC may also be referred to as relaxed or slow vital capacity (SVC). For completeness it is appropriate to quote FVC and VC as although in normal individuals a small difference can be present in VC and FVC, this is notably exaggerated, with FVC comparatively lower than VC, in those

with airflow obstruction reflecting hyperinflation and air trapping. In addition, as VC should be better than FVC, if a large difference is present between the 2 measurements with VC being lower than FVC, this could indicate an imperfect procedure.

Measurements of FEF25-75% provide information about the small airways and a reduction in this measurement can be an early change reflecting airflow obstruction in these small airways (Ranu et al., 2011, Pellegrino et al., 2005). While a reduction was noted in FEF25-75 % predicted in both groups, the median %predicted in the non-smokers was still above 80% whilst the smokers however had a median FEF25-75 %predicted of 61.50 indicating more involvement in small airways in the smokers group. Median PEF% predicted in both groups was above 97% and indeed exceeded 100% in the non-smokers group.

Focusing on median lung volumes, both RV and TLC % predicted in both the smokers and non-smokers groups exceeded 100%. Whilst measurement of RV and TLC are essential in the accurate diagnosis of restrictive lung disorders characterised by a reduction in TLC, they are also very useful in diagnosing obstructive lung diseases where an increase in RV, suggests air trapping, TLC or the RV/TLC ratio may suggest the presence of obstruction (Pellegrino et al., 2005). Both the non-smokers and the smokers had median results which may suggest air trapping with RV % predicted >120% and RV/TLC % observed >40% in both groups.

Whilst looking at the medians for variables in each group is important, it is arguably more informative to look at the pattern of lung dysfunction to ascertain if each individual has a normal, obstructive, restrictive or mixed (obstructive and restrictive) pattern of lung function. Obstructive lung function is indicated by a FEV1/FVC <70%, restrictive lung function is indicated by a FEV1/FVC >70% and FVC <80% predicted, but most importantly a TLC <80% predicted. Mixed ventilatory defects are the co-occurrence of both obstruction and restriction with reduced FEV1/FVC and reduced TLC. The measurement of TLC is necessary to accurately diagnose a mixed defect as VC or FVC can be reduced in both restriction and obstruction. Table 8, below, summarises the patterns of lung function in the non-smokers and smokers groups.

	Non smokers N=64 Number (%)	Smokers N=36 Number (%)
Normal lung function	44 (68.75%)	17 (47.22%)
Obstructive lung function	18 (28.13%)	18 (50.00%)
Restrictive lung function	2 (3.13%)	1 (2.78%)
Mixed obstructive and restrictive lung function	0 (0.00%)	0 (0.00%)

Table 8: Summary of pattern of lung function in non-smokers and smokers

Those individuals categorised as having normal lung function all had FEV1/FVC ≥70% and a TLC ≥80% predicted. Those individuals classed as having obstructive lung function all had a FEV1/FVC <70% and a TLC ≥80% predicted. Two participants in the non-smokers group were classed as having restrictive lung function and one in the smokers group was classed as having restrictive lung function. These 3 participants warrant further explanation and results interpretation, in these 3, with caution. One of these 2 participants in the non-smokers group had a FEV1/FVC of 79.56%, FEV1/VC of 81.59% and a FVC of 71% predicted and as such had spirometric evidence of restriction, however this was the same participant in which the gold standard to assess restriction, TLC, could not be measured as he was too dyskinetic. The other participant in the non-smokers group classed as restriction based on TLC had spirometry results that were not consistent with restriction or obstruction, with a TLC of 78% predicted, FEV1/FVC of 78.88%, FEV1/VC of 78.95% and a FVC of 87% predicted. Similarly to the last participant, the individual in the smokers group categorised as restriction on TLC, with a TLC of 75% predicted, had a normal FEV1/FVC, normal FEV1/VC and a FVC >100% predicted.

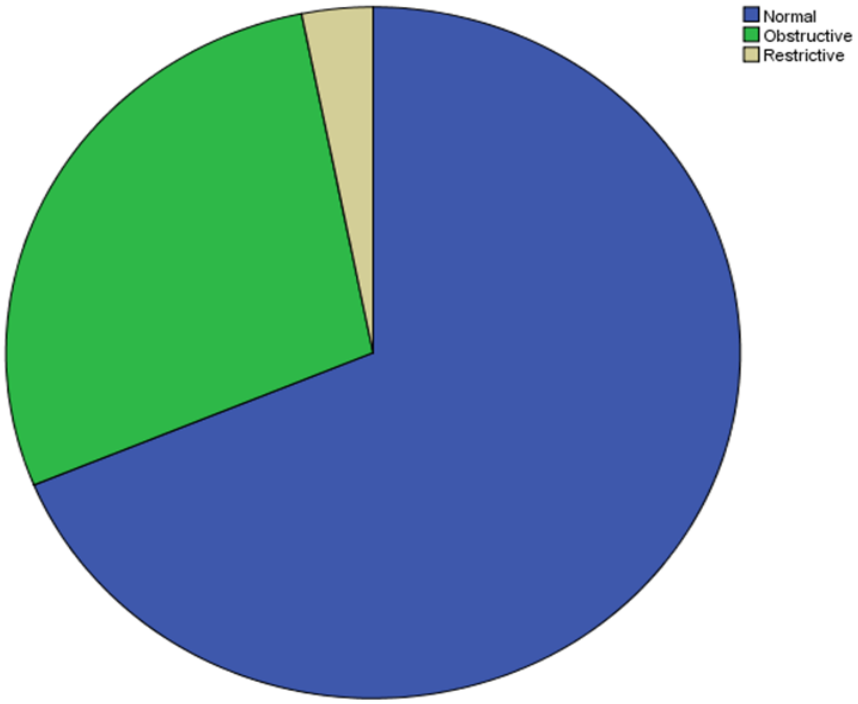

Figure 16: Pattern of lung function in non-smokers

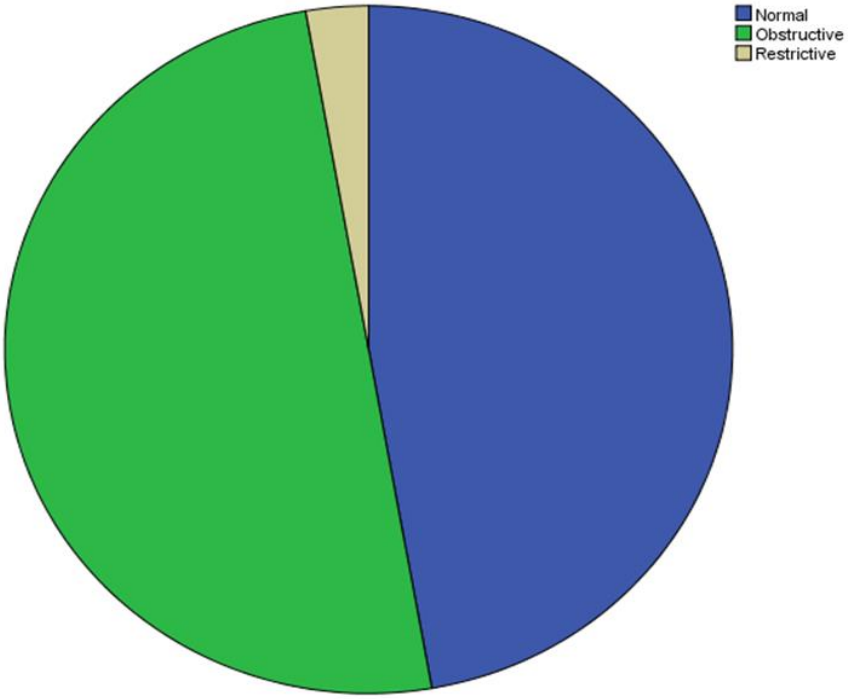

Figure 17: Pattern of lung function in smokers

As highlighted in table 8 and figures 16 and 17, 68.75% of the non-smokers group and 47.22% of the smokers group had normal lung function, however 28.13% of the non-smokers group and 50.00% of the smokers group had spirometric evidence of obstruction. As discussed in section 2.3.2, when airflow obstruction is identified with a FEV1/FVC <0.7, this can be further categorised

into severity according to the reduction in FEV1. Categorised based on FEV1 %predicted; ≥80% mild or stage 1, 50-79% moderate or stage 2, 30-49% severe or stage 3, <30% very severe or stage 4 whilst noting that symptoms should be present to diagnose someone with COPD if FEV1 %predicted is ≥80% (NICE, 2010). Table 9 below, categorises the severity of the obstruction in those with a FEV1/FVC <70% in each group.

	Non-smokers with obstruction N = 18 Number (%)	Smokers with obstruction N = 18 Number (%)
FEV1 ≥80% Stage 1 Mild	16 (88.89%)	12 (66.67%)
FEV1 50 – 79% Stage 2 Moderate	2 (11.11%)	5 (27.78%)
FEV1 30 – 49% Stage 3 Severe	0 (0.00%)	1 (5.56%)
FEV1 <30% Stage 4 Very severe	0 (0.00%)	0 (0.00%)

Table 9: Severity of obstruction in non-smokers and smokers with obstructive spirometry

In both the non-smokers and smokers with obstructive spirometry, the severities were mild to moderate (stage 1 to stage 2) predominantly, with the highest percentages in both groups being classified as stage 1 or mild. Focusing on the severity of the obstruction to airflow there was an interesting finding in our patient demographic of a tendency towards supranormal values when the variables of FEV1 % predicted and FVC % predicted were looked at in isolation. In the non-smokers group, of the 44 with normal lung function, 34 had a FEV1 of >100% predicted and 34 had a FVC of >100% predicted. In the smokers group, of the 17 with normal lung function, 11 had a FEV1 of >100% predicted and 12 had a FVC of >100% predicted. In the non-smokers group, of the 18 with obstructive lung function, 7 had a FEV1 of >100% predicted and 15 had a

FVC of >100% predicted. In the smokers group, of the 18 with obstructive lung function, 7 had a FEV1 >100% predicted and 13 had a FVC of >100% predicted. Thus, particularly thinking about those with obstructive spirometry, whilst the individual volumes may have been supranormal in some cases, the ratio of the FEV1/FVC still indicates obstruction to airflow in the volume that can be forcibly exhaled in the first second.

Being cautious not to continually dichotomise to increasingly small numbers; tables 10 and 11, below, report the demographics, disease phenotype, UPDRS, PDQ39 summary index, HADS and SCOPA-SLEEP results for the non-smokers with normal and obstructive spirometry and the smokers with normal and obstructive spirometry. Although not a recognised score in its own right, a "bulbar score" was devised from UPDRS questions. Question 3.1 of the UPDRS is an objective assessment of speech and was hence used as an objective bulbar score. Questions 2.1, 2.2 and 2.3 of the UPDRS are subjective assessments of speech, saliva, drooling, chewing and swallowing, hence were used as a subjective bulbar score. An overall bulbar score was calculated by adding the objective and subjective bulbar score results. As per the UPDRS, worse signs and symptoms are reflected by higher scores. With the exception of disease phenotype, where numbers of individuals were reported, the values reported are medians and interquartile ranges.

Due to the numbers when dichotomised the tables were interpreted with caution. An interesting finding was the higher percentage of tremor dominant motor phenotype in the non-smokers obstructive lung function group, the other 3 groups all had a higher percentage of PIGD phenotype which was most likely a representation that there were simply higher numbers of PIGD phenotype patients across the whole study (Of 100 patients; 65 were PIGD phenotype, 27 were TD phenotype and 8 indeterminate motor phenotype). The smokers with obstructive lung function scored highest across all domains in the SCOPA-SLEEP assessment suggesting poorer sleep at night and increased sleepiness during the day and evening. Both smokers groups, normal and obstructive lung function, had higher depression ratings than the comparative non- smokers.

	Non-Smokers Normal lung function N = 44	Non-smokers Obstructive lung function N = 18	Smokers Normal lung function N = 17	Smokers Obstructive lung function N = 18
Age (years)	67.00 (62.75 – 73.00)	71.50 (68.00 – 77.75)	68.00 (63.00 – 75.00)	72.50 (67.50 – 76.75)
Disease duration (months)	58.50 (23.00 – 89.50)	41.50 (19.00 – 63.75)	49.00 (14.00 – 87.00)	51.50 (17.25 – 108.00)
PIGD phenotype	27 (61.36%)	8 (44.44%)	13 (76.47%)	14 (77.78%)
TD Phenotype	11 (25.00%)	10 (55.56%)	4 (23.53%)	2 (11.11%)
Indeterminate Phenotype	6 (13.64%)	0 (0.00%)	0 (0.00%)	2 (11.11%)
Bulbar score Objective	1.00 (0.00 – 1.00)	1.00 (1.00 – 1.00)	1.00 (1.00 – 2.00)	1.00 (0.00 – 1.00)
Bulbar score Subjective	2.00 (0.00 – 4.00)	2.00 (0.25 – 3.00)	2.00 (1.00 – 5.00)	2.00 (1.00 – 3.00)
Total bulbar score	2.50 (1.00 – 5.00)	3.00 (1.25 – 4.00)	3.00 (2.00 – 6.00)	3.00 (1.00 – 4.00)
UPDRS Part 1	7.00 (4.75 – 13.00)	6.50 (4.00 – 12.00)	11.00 (8.00 – 13.00)	12.50 (9.00 – 15.50)
UPDRS Part 2	9.00 (5.75 – 15.00)	9.00 (5.25 – 14.50)	15.00 (12.00 – 19.00)	11.00 (8.25 – 18.75)
UPDRS Part 3	24.50 (19.75 – 31.50)	35.00 (28.25 – 37.00)	37.00 (27.00 – 40.00)	23.00 (20.00 – 41.75)
Hoehn and Yahr	2.00 (2.00 – 2.00)	2.00 (2.00 – 2.00)	2.00 (2.00 – 2.00)	2.00 (2.00 – 3.75)
UPDRS Part 4	0.50 (0.00 – 4.00)	0.00 (0.00 – 0.75)	0.00 (0.00 – 4.00)	0.00 (0.00 – 3.00)

Table 10: Demographics, motor phenotype and UPDRS scores comparison; non-smokers and smokers, normal lung function and obstructive lung function

	Non-Smokers Normal lung function N = 44	Non-smokers Obstructive lung function N = 18	Smokers Normal lung function N = 17	Smokers Obstructive lung function N = 18
PDQ 39 SI	12.03 (7.84 – 29.61)	13.23 (6.25 – 25.63)	22.73 (14.95 – 34.75)	23.59 (14.41 – 33.93)
SCOPA B	5.00 (2.00 – 8.00)	3.00 (2.25 – 4.75)	2.00 (0.75 – 7.25)	5.50 (3.25 – 7.75)
SCOPA C	3.50 (2.00 – 4.00)	2.50 (2.00 – 3.75)	2.00 (1.00 – 4.25)	3.50 (1.25 – 4.00)
SCOPA D	3.00 (2.00 – 5.25)	4.00 (2.00 – 5.75)	4.00 (2.00 – 5.00)	4.00 (4.00 – 7.00)
HADS A	4.00 (2.00 – 6.00)	3.00 (1.00 – 5.00)	4.00 (2.00 – 8.00)	3.00 (2.00 – 7.00)
HADS D	3.00 (2.00 – 5.50)	3.00 (3.00 – 6.00)	8.00 (3.00 – 8.00)	6.50 (3.50 – 8.00)

Table 11: PDQ-39, SCOPA-SLEEP and HADS scores comparison; non-smokers and smokers, normal lung function and obstructive lung function

As extensively discussed in section 2.3.3, the shape of maximal flow volume loops can be helpful in diagnosing an upper airway obstruction (UAO) and differentiating this from lower airway. The shape can help classify the location, being extrathoracic or intrathoracic, and the nature, being fixed or variable of the obstruction. With variable extrathoracic UAO the obstruction is worse during inspiration as the pressure inside the trachea falls on inspiration, thus flattening is seen of the inspiratory portion of the flow volume loop. Patterns of UAO can also be seen on the flow-volume loops as a respiratory flutter, with regular consecutive flow accelerations and decelerations (in a saw tooth pattern), or irregular abrupt changes in flow often dropping to zero.

Whilst the shape of the flow volume loop is most useful in the detection of UAO, some numerical indices are also helpful in the indication of UAO. With numerical indices there is variation in terminology and values used between previous authors, such as the value above which FEV1/PEF indicates UAO. There are also not widely accepted numerical criteria to diagnose UAO e.g. an individual must have “x” many positive indices for a diagnosis of UAO thus the

indices are indicators. As previously discussed, the numerical parameters also reflect different types of UAO e.g. fixed extrathoracic UAO presents with decreased PEF, decreased MIF50 and MIF50/MEF50 ~1; variable extrathoracic UAO normal or decreased PEF, decreased MIF50 and MIF50/MEF50 <1; while intrathoracic UAO demonstrated decreased PEF, normal or decreased MIF50 and MIF50/MEF50 >1 (Pellegrino et al., 2005). Due to the nature of PD, it could be postulated that we would be looking for potential variable extrathoracic UAO. For this study, numerical indicators of UAO were considered to include FEV1/PEF >8ml/l/min, MEF50/MIF50 >1 (i.e. MIF50/MEF50 <1), PIF<3l/sec, FEV1/FEV0.5 >1.5, PEF/MEF50 <2 and reduced PEF (<80% predicted).
As described in section 3.5, all pulmonary function testing was performed by qualified, experienced respiratory physiologists accredited to the ARTP. When the initial flow volume loop results were reviewed it was evident that all respiratory physiologists were aware they had to do maximal expiratory flow volume loops but not all were aware they were requested to do maximal inspiratory loops also, which has to be born in mind when interpreting the inspiratory results of the flow volume loops. The results from any loops that were obviously not maximal efforts were not included in the reporting. Table 12 below, reports the prevalence in numbers and percentages of each afore mentioned UAO criteria in the non-smokers and the smokers. All participants in both groups had complete results for flow oscillations, flattened inspiratory loop, abrupt flow changes, FEV1/PEF, PEF <80% predicted and PEF/MEF50. One participant in the non-smokers group did not have a FEV0.5 recorded thus one FEV1/FEV0.5 result was missing from the non-smokers group. As highlighted above, 11 of the non-smokers and 3 of the smokers inspiratory loops were obviously not maximal efforts and were thus not included, thus for these 14 participants PIF and MIF50 were not recorded. Table 12 details the actual numbers in each group demonstrating the particular UAO criteria. The percentages reported in table 12 are percentages of individuals with available results e.g. for non-smokers with a PIF<3l/s that represents 15 of 53 with inspiratory loop results.

	Non smokers N=64 Number (%)	Smokers N=36 Number (%)
Flow oscillations	39 (60.94%)	19 (52.78%)
Flow oscillations (marked)	19 (29.69%)	7 (19.44%)
Flattened inspiratory loop	24 (37.50%)	14 (38.89%)
Abrupt flow changes	11 (17.19%)	9 (25.00%)
FEV1/PEF > 8ml/l/min	7 (10.94%)	3 (8.33%)
PEF/MEF50 < 2	22 (34.38%)	8 (22.22%)
PEF < 80% predicted	11 (17.19%	9 (25.00%)
PIF < 3l/s	15 (28.30%)	9 (27.27%)
FEV1/FEV0.5 > 1.5	2 (3.17%)	3 (8.33%)
MEF50/MIF50 > 1	20 (37.74%)	6 (18.18%)

Table 12: Prevalence of indicators of UAO in non-smokers and smokers

The above table illustrates high percentages across both the non-smokers and smokers groups of individual visual qualitative and also quantitative indicators of UAO. Importantly both groups demonstrated high prevalence of UAO indicators, not just smokers. Table 12 reports the prevalence of each UAO criteria, however it is important acknowledge that each individual participant may have more than 1 of the 9 criteria. It would be expected that increasing numbers of UAO criteria per individual makes a clinically significant diagnosis of UAO more likely. Table 13 and figure 18 below, illustrate the frequency in the non-smokers and smokers groups of those with a total of 0, 1, 2 and 3 or more UAO criteria.

With respect to the visual criteria, those with marked rather than more subtle flow oscillations were regarded as a positive result. It has to be acknowledged also that these results may be under reporting the numbers in each individual for 2 reasons; as highlighted above ensuring the flow oscillations were marked and as the 14 individuals whose inspiratory results were discounted are also included in the below numbers.

	Non smokers N=64 Number (%)	Smokers N=36 Number (%)
UAO 3 or more criteria	20 (31.25%)	9 (25.00%)
UAO 2 criteria	18 (28.13%)	12 (33.33%)
UAO 1 criteria	15 (23.44%)	8 (22.22%)
UAO 0 criteria	11 (17.19%)	7 (19.44%)

Table 13: Cumulative numbers of UAO criteria in non-smokers and smokers

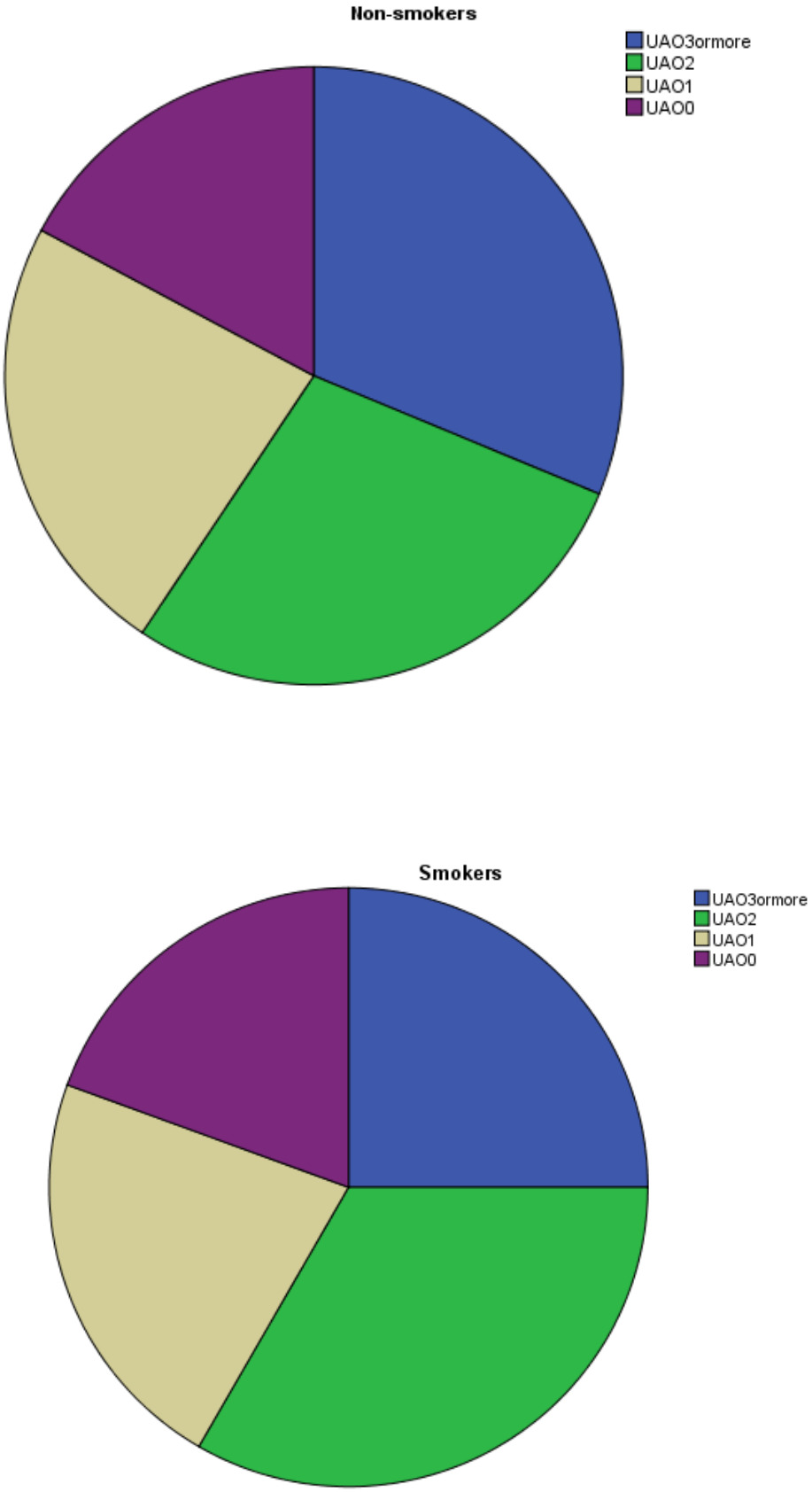

Figure 18: Cumulative numbers of UAO criteria in non-smokers and smokers

Cumulative numbers of UAO criteria in both the non-smokers and smokers are high with it being more common to have criteria indicating UAO than no indicators of UAO. In the non-smokers and smokers groups, 31.25% and 25.00% respectively had 3 or more criteria of UAO, which is also a probable underestimation. Noting the higher number in the non-smokers and those without known obstructive lung disease indicates this result cannot be attributed to smoking, COPD or asthma.

Finally in the pulmonary function test results section, as discussed in section 2.3.6, respiratory muscle function tests should be performed as part of a more comprehensive diagnostic process and respiratory muscle dysfunction is to be differentiated from lung function abnormalities (Troosters et al., 2005). In generalised neuromuscular disorders it is unusual for the respiratory muscles to be unaffected (Polkey et al., 1995). The maximal expiratory pressure and maximal inspiratory pressure measured at the mouth are abbreviated to MEP and MIP respectively and sniff nasal inspiratory pressure to SNIP. In normal subjects maximal expiratory pressures are expected to be higher than inspiratory pressures, however SNIP results are generally higher than MIP results (Troosters et al., 2005, Fitting, 2006). Table 14 below, illustrates the median values and interquartile ranges of the percent predicted MEP, MIP and SNIP results for the non-smokers and smokers.

	Non smokers N=64 Median (IQR)	Smokers N=36 Median (IQR)
MEP % predicted	82.34 (58.55 – 98.42)	96.82 (80.74 – 105.20)
MIP % predicted	79.02 (57.80 – 92.53)	82.21 (69.70 – 102.08)
SNIP % predicted	58.53 (35.89 – 81.50)	63.96 (43.30 – 82.81)

Table 14: Respiratory muscle strength in non-smokers and smokers

The results of the respiratory muscle strength tests are illustrated as percent predicted values and thus take into account that values for expiratory muscle tests are usually higher than inspiratory muscle tests. In both the non-smokers

and smokers inspiratory muscle function seems to be more affected and impaired than expiratory muscle function. Unlike normal individuals, SNIP percent predicted results are worse than MIP results in both the non-smokers and smokers. Interestingly the percent predicted MEP, MIP and SNIP median values are worse in all 3 domains in the non-smokers compared to the smokers, noting that the smoker's median percent predicted MEP is greater than 96%. The pulmonary function and respiratory muscle strength tests have yielded some fascinating results in this cross-sectional study and will be discussed in detail.

4.4.1 Discussion

Pulmonary function and respiratory muscle strength tests should be performed as part of a comprehensive diagnostic process and each of the tests complement each other to aid in diagnostic accuracy. As such it is appropriate to discuss the results together. The PFT and respiratory muscle strength tests have yielded very interesting, surprising and novel results.

Twenty seven studies were reviewed in section 2.3.9, Pulmonary function in Parkinson's disease, however it is difficult to compare these due to the different assessments and outcome variables, for example some studies only looked at respiratory muscle strength tests and not spirometry. Studies that looked at spirometry, with or without body plethysmography, tended to report the percentage of or number of participants with either normal, restrictive or obstructive lung function. Eight of the studies reported the predominant pattern of respiratory dysfunction seen in PD was restriction, these were predominantly more recent studies (Izquierdo-Alonso et al., 1994, De Pandis et al., 2002, Weiner et al., 2002, Cardoso and Pereira, 2002, Sathyaprabha et al., 2005, Pal et al., 2007, Shaheen H.A., 2009, Wang et al., 2014). Of these 8 studies only 1 performed body plethysmography for measurement of TLC, however they reported their findings of restrictive dysfunction based on the spirometry findings not TLC (Wang et al., 2014).

Based on the findings of restrictive lung function in a number of neuromuscular diseases, e.g. muscular dystrophy and amyotrophic lateral sclerosis, and previous research, particularly in more recent years, of lung function in PD pointing towards restrictive spirometry it would not be unreasonable to consider this as a likely potential result of PFT testing in PD. The results however have

indicated that this is not the case in our patient demographic. Highlighted in tables 7 and 8, with reduced TLC being the gold standard for diagnosing restriction, both the non-smokers and smokers had median TLCs of over 100% predicted and only 3 participants out of 100 were diagnosed as having restrictive lung function. One of these diagnoses was based on the results of FEV1 and FVC alone, without TLC, as the patient was too dyskinetic to tolerate lung volume testing. Thus the prevalence of restrictive lung function in our group is very low. As mentioned this is contrary to a number of previous studies of lung function in PD. Most previous studies based their diagnoses of restriction on spirometry variables, FEV1 and FVC, alone without the benefit of lung volumes. Poor instruction, poor technique and insufficient effort can produce low FEV1 and FVC values with a ratio diagnostic of restriction and thus give false positive results. Given the findings in this study using gold standard tests performed by qualified, experienced respiratory physiologists accredited to the ARTP, it is likely that in this demographic restriction is rare and that previous studies have produced false positive results by not basing the conclusions on TLC. Interestingly, of the 27 studies reviewed in section 2.3.9, Pulmonary function in Parkinson's disease, only 5 studies recorded TLC measurements. Of these 5 studies, 1 reported the finding of predominantly normal lung function, 2 predominantly obstructive dysfunction, 1 reported from 58 patients 18 had obstructive dysfunction and 16 had restrictive dysfunction and finally 1 reported predominantly restrictive dysfunction (Obenour et al., 1972, Sabate et al., 1996a, Sabate et al., 1996b, Mikaelee et al., 2006, Seccombe et al., 2011, Wang et al., 2014). The 1 study that measured TLC and reported a predominantly restrictive pattern of pulmonary dysfunction based this on spirometry results and not the TLC results. Looking at the graphical representation of the TLC results in the afore mentioned paper this was not consistent with a finding of restrictive dysfunction (Wang et al., 2014).
Whilst 44 (68.75%) of the non-smokers and 17 (47.22%) of the smokers had normal lung function, 18 (28.13%) of the non-smokers and 18 (50.00%) of the smokers had obstructive lung function. No participants had mixed obstructive and restrictive pictures. It is an expected finding of a high prevalence of obstruction in those with known asthma or COPD and those with a known significant smoking history. With only 50% in the smokers group demonstrating obstructive spirometry it does however raise the question of previous accurate

diagnoses of those labelled with obstructive lung disease. An unexpected finding was in the non-smokers that over 25% had obstruction based on FEV1/FVC ratio. This result is even more interesting when the severity of the obstruction is categorised as highlighted in table 9. Of the 18 non-smokers with obstructive spirometry, 16 (88.89%) were categorised as stage 1 or mild with a FEV1 ≥80% predicted. Of these, 7 had a FEV1 of >100% predicted. As reported in table 7, when looking at FEV1 and FVC in isolation and not as a ratio there is a tendency towards supranormal results with the median FEV1 and median FVC results, in both the smokers and non-smokers, being more than 100% predicted. In the non-smokers with normal lung function, 34 out of 44 had a FEV1 and FVC of >100% predicted and in the smokers with normal lung function, 11 had a FEV1 of >100% predicted and 12 had a FVC of >100% predicted. In addition to questioning the previous diagnoses of some of those diagnosed with obstructive lung disease these findings raise questions; why does there seem to be a high prevalence of supranormal (>100% predicted) values of FEV1 and FVC in this population and why do over 25% of non-smokers with PD have obstructive spirometry?

In this study “supranormal” values are described as those >100% predicted, and whilst it is unlikely that values less than 120% predicted are clinically relevantly “supranormal”, these are interesting findings none the less. These supranormal FEV1 and FVC values also further add evidence that restriction is not a typical characteristic in this demographic. It could be postulated that the reference (predicted) equations used in this study, and routinely in clinical practice, of European Community for Coal and Steel (ECCS) published in 1993, may be out of date and do not reflect current populations. As described in section 2.2.2, dating back over 30 years, prospective and retrospective studies have demonstrated an inverse correlation between PD and smoking concluding a reduced risk of developing PD in smokers. With this in mind, the individuals with PD in this study may represent a large proportion of those with no direct smoking or passive smoking history and resultant supranormal FEV1 and FVC values.

Over 25% of the non-smokers group had evidence of obstruction based on the ratio of FEV1/FVC. Whilst in this group the individual measurements of FEV1 and FVC in some participants may have been normal or supranormal, the ratio of FEV1/FVC still indicated obstruction to airflow in the volume that could be

forcibly exhaled in the first second compared to the FVC. Obstructive lung disease is characterised by lower airway obstruction and is caused by any disease that obstructs the airflow, for example by narrowing the airways (e.g. asthma). An obstructive ventilatory defect is represented by a disproportionate reduction in expiratory maximal airflow in relation to maximal volume, i.e. FEV1 is reduced more than FVC and thus FEV1/FVC is lowered (Ranu et al., 2011, Pellegrino et al., 2005). This reduction in the volume of air that can be forcibly exhaled in the first second suggests airway narrowing during exhalation (Pellegrino et al., 2005). Generating maximal flows during FVC manoeuvres requires rapid activation of appropriate driving pressures by respiratory muscles, coordinated with stabilisation of extrathoracic airway muscles to optimise the dimensions of, and flow through, the extrathoracic airway. With this in mind, could upper airway obstruction (UAO) be sufficiently severe to limit airflow and demonstrate obstructive spirometry or is the obstruction from, or contributed to by, another site. As highlighted in the results there is evidence of UAO which will be further discussed in detail, however noting the median results of FEF25-75 % predicted of 83.50% and 61.50% in the non-smokers and smokers respectively purely attributing obstructive spirometry to UAO may not be appropriate. Although the FEF25-75 was above 80% predicted in the non-smokers, as reported in table 7, noting the other supranormal values in this demographic this may reflect a reduction. Changes in FEF25-75 provide information about the small airways and a reduction in this measurement is often an early change reflecting airflow obstruction in these small airways. Thus other contributors to obstruction need to be considered. The majority of PD patients have symptoms or signs of dysautonomia. Dysfunction of components of the autonomic nervous system (ANS) can produce characteristic clinical signs and symptoms. Cardiovascular dysautonomia is commonly reviewed where as other dysautonomias may be overlooked (Goldstein, 2014). Dysautonomia of the respiratory system does not appear to be researched in PD but could easily be a cause of obstruction. Bronchial smooth muscle and mucous glands both affect the diameter of airways and thus resistance to airflow, i.e. obstruction. The afore mentioned are also the targets of the ANS within the respiratory system with the upper thoracic sympathetic ganglia, and the dorsal motor nucleus of the vagus providing the autonomic nerves to the airways. The parasympathetic ganglia found in the bronchi and bronchioles

innervate airway smooth muscle and glands. The parasympathetic innervation of bronchial smooth muscle is greater than that of the sympathetic system and stimulation of the vagus causes bronchoconstriction and the vagus also causes secretion of mucus. Thus it could be postulated that dysautonomia associated with PD causing parasympathetic over activity could be the cause of airway narrowing, increased resistance to airflow and the subsequent obstructive spirometry.

Consideration of possible causes of obstruction also need to be reflected back to the pathophysiology of PD, particularly alpha-synuclein and Lewy pathology. As already discussed Lewy pathology is not restricted to the brain and has also been found to affect the autonomic nervous system, including the cardiovascular autonomic system. There is increasing research and interest in the involvement of the enteric nervous system and early positive biopsies of the gastrointestinal system (Braak et al., 2003, Hawkes et al., 2007, Lebouvier et al., 2010). Questions do still remain surrounding why not all individuals with PD suffer autonomic dysfunction and why presence of pathology does not always translate into symptoms (Ferrer, 2011). However despite the interest in Lewy body formation in the bowel, there seems to have been little or no research looking at potential Lewy body formation and lung and airway parenchyma. Previous cellular research reported that in addition to a presynaptic nerve terminal protein, alpha-synuclein is also expressed in cultured human astrocytes and its levels are increased by stimulation with interleukin-1beta. This suggests it has potential involvement in inflammatory processes and immune responses. The authors further investigated the effect of inflammatory stimuli on alpha-synuclein expression in human macrophages and particularly noted that alpha-synuclein immunoreactivity was present in alveolar macrophages from human lung tissues (Tanji et al., 2002). This potential involvement of alpha-synuclein in inflammatory processes and presence in the lung could feasible contribute to airway obstruction.

Focusing on a more clinical level, the cardinal features and motor symptoms of PD; bradykinesia, tremor and rigidity, could be causing obstructive lung function. Bradykinesia being slowness of movement and hypokinesia meaning movements are small in addition to being slow. Rigidity is frequently described as “lead pipe rigidity” and may be felt in the limbs or more proximally, termed axial rigidity, in the neck and trunk. Tremor can be frequently evident in the legs,

lips, chin and jaw and patients often describe a sensation of internal tremor, a feeling of tremor inside the chest, abdomen, arms, or legs that cannot be seen on the outside (Shulman et al., 1996). Pulmonary function testing tests many effort dependent variables and also those over a timed period. Focusing on FEV1 and the ratio of FEV1/FVC that represents obstruction, is represented by a comparatively lower (more affected) FEV1 than FVC. The slowness of movement of bradykinesia and potential start hesitation may affect the recording of FEV1, as this is a measurement over the first 1 second of the procedure, more markedly than it affects FVC resulting in lower FEV1 than would be expected and thus resultant obstruction. Air flow, particularly when considering the upper airways, requires considerable coordination to achieve maximal flow and no restriction to the flow. Tremor, rigidity and bradykinesia could contribute to disorganised movements of respiratory muscles that become important variables in inducing obstruction. It is important to acknowledge when considering FEV1 and PEF measurements, the initial 25-33% of FVC exhaled depends primarily on muscular effort rather than the mechanical characteristics of the lungs and hence these measurements also reflect the calibre of the central airways and force exerted by expiratory muscles and this initial activation could be impaired by the clinical features of PD. It also has to be considered that disorganised movements of the respiratory muscles could be caused by dyskinesia, dystonia and medication and also affect lung function. Upper airways obstruction warrants a significant amount of discussion and consideration if involvement of the upper airway musculature is significantly severe enough to limit air flow.

The upper airway can be considered to extend from the mouth to the carina, subdivided into extrathoracic and intrathoracic portions. During inspiration, the intrathoracic airways expand with the expanding lungs and the calibre of extrathoracic airways diminishes in caliber due to their intraluminal pressure being lower than the atmospheric pressure. During expiration this pattern is reversed. Large airway flow is turbulent and this turbulence increases if the diameter of the airway reduces. As extensively discussed in section 2.3.3, the most useful indicator of UAO is visual inspection of the flow volume loop. Numeric indices can be indicators of UAO and those highlighted in table 12 represent different aspects of UAO however no “formula” as such exists to define UAO from a combination of numerical indices, they are however

indicators. It would stand to reason that the more numeric indicators of UAO an individual demonstrates the more likely that this is clinically significant.
Focusing on tables 12 and 13 and on figure 18, the most striking feature is the prevalence of visual and numeric indicators of UAO and the cumulative numbers of indicators in each individual. Each numeric indicator of UAO is seen in between 3.17% and 37.74% of non-smokers and 8.33% and 27.27% of smokers. In the non-smokers the most commonly seen numeric indicator is MEF50/MIF50 >1 and in the smokers is PIF <3l/s. Reflecting back to flow volume loops, these 2 indicators suggest the inspiratory portion is more affected which would be seen in variable extrathoracic UAO. This finding is supported by visual inspection for flattened inspiratory loop which was seen in 37.50% and 38.89% of non-smokers and smokers respectively. Other visual indicators of UAO were even more commonly seen, with flow oscillations “saw tooth” seen in 60.94% (marked in 29.69%) and 52.78% (marked in 19.44%) of non-smokers and smokers respectively. Abrupt flow changes were seen in 17.19% of non-smokers and 25.00% of smokers. Cumulative numbers of UAO criteria were high in both groups with it being more common to have criteria indicating UAO than no indicators of UAO. Given the highlighted prevalence of UAO in this group it is entirely feasible that involvement of the upper airway musculature is significantly severe enough to limit air flow and demonstrate obstructive spirometry.
Thus it has to be considered why and what causes UAO and turbulent airflow to be so prevalent in this patient demographic. The intrathoracic airway has the relative protection of the thoracic cage, however the extrathoracic airway is surrounded closely by muscles required for respiration and the accessory muscles in the neck. It is known that PD demonstrates axial involvement and thus it is more than feasible that these muscles are affected. Bradykinesia and rigidity of these muscles could lead to UAO and given that muscle dysfunction in PD is often asymmetrical, this may lead to laterality of muscles and different muscles affected in asymmetrical ways which may cause distortion of the upper airway and disorganised movements subsequently causing UAO. Abrupt changes, at times down to baseline on the flow volume loops, suggest intermittent airway closure which again may be caused by disorganised upper airway musculature movement. Dyskinesia seen in some individuals with PD may also potential involve the upper airway musculature and cause abrupt

changes and distortions. Given the pathophysiology of PD and clinical signs of tremor, it is likely that regular “saw tooth” oscillations causing UAO are caused by tremor of the upper airway musculature. It has to be born in mind, particularly when considering symptoms and future research, this finding was historically believed to be predominantly characteristic of the upper-airway narrowing seen in obstructive sleep apnoea (OSA). The intermittent nocturnal hypopharyngeal obstruction in OSA is probably the commonest form of UAO and flow volume loops in these patients may have this “saw tooth” sign of regular oscillations (Krieger et al., 1985).

Finally respiratory muscle function tests are to be considered, importantly as it is very unusual for respiratory muscles to be spared in neuromuscular disorders. In normal individuals, expiratory pressures are higher than inspiratory pressures and SNIP results are generally higher than MIP results. As detailed in table 14 the respiratory muscle strength tests in this demographic revealed very interesting results. The smokers group demonstrated higher percent predicted values than the non-smokers in all the expiratory and inspiratory strength tests. This is in itself an interesting finding with various potential causes for this; it may be that the severity of axial disease involvement in this group was less or even chronic respiratory symptoms have conditioned these muscles for example for stronger cough. In both the non-smokers and smokers, inspiratory results were worse than expiratory results; with median MEP percent predicted of 82.34 and 96.82, MIP of 79.02 and 82.21 and SNIP of 58.53 and 63.96 in non-smokers and smokers respectively. As discussed in section 2.3.6 severe generalised respiratory muscle weakness manifests as breathlessness and tachypnoea and nocturnal hypoventilation disturbs sleep, cognitive function and causes daytime somnolence, finally resulting in ventilatory failure and cor pulmonale. Inspiratory muscle weakness tends to cause dyspnoea and poor exercise tolerance, while expiratory muscle and bulbar weakness leads to speech problems, impaired cough and predisposes to mucus retention, pneumonia and aspiration.

Two interesting features warrant further discussion; why is SNIP worse than MIP and why are inspiratory muscles seemingly more affected than expiratory muscles? It would be expected that SNIP results would be higher than MIP but the opposite was true in our population. Considering the Braak hypothesis and olfactory bulb involvement in PD it may be postulated that these patients struggle to perform the SNIP manoeuvre. Another possibility is the effect of start

hesitation and bradykinesia; SNIP is a ballistic manoeuvre requiring immediate activation and force with the highest value recorded, where as MIP is a sustained over 1 second measurement. Given the pathophysiology of PD it is possible that the ballistic nature of a SNIP manoeuvre is more difficult for this group. Inspiratory muscles being more affected than expiratory muscles is a fascinating finding as it has previously been suggested that in the presence of disease the inspiratory muscles may lose less strength than the expiratory muscles due to baseline EMG activity of inspiratory muscles always being greater than that of expiratory muscles during quiet breathing with the inspiratory and expiratory muscles assuming different roles within the breathing cycle; during tidal volume breathing the inspiratory muscles have constant activation, whilst abdominal/expiratory muscles assume less of a role because expiration during tidal breathing is due to passive recoil (De Troyer and Estenne, 1984, Silverman et al., 2006). The worse inspiratory results in this demographic may be due to the asymmetric nature of PD and a tendency to not affect all muscles equally and could also be due to difficulty coordinating muscular manoeuvres, particularly unfamiliar ones, with MIP being a less intuitive and automatic procedure than MEP.

The results of the cross-sectional study have shown a notable prevalence of obstruction, upper airways obstruction and inspiratory muscle weakness in this population. This pattern of dysfunction of the respiratory system could lead to increased morbidity and mortality. With inspiratory muscle weakness individuals could suffer dyspnoea, hypoxia, tachypnoea, increased respiratory infections reduced exercise tolerance and impaired functional capacity. Speaking and swallowing require coordinated, precise upper airway movements; UAO could contribute to speech and swallowing difficulties, hypophonia, sleep disordered breathing, excessive daytime somnolence, acute respiratory failure and difficulty in extubation. Given these significant findings, further research is warranted to assess the benefit of rehabilitation of the pulmonary system, both pharmacologically and non-pharmacologically. The effect of dopaminergic treatment on pulmonary function needs to be assessed in detail and rehabilitation, by general and specific inspiratory muscle training, warrants significant further study.

4.5 Strengths and limitations

The cross-sectional study had both strengths and limitations. The study had a significant amount of strengths which most notably included; the largest study to date in pulmonary function in PD, dichotomising but including both smokers and non-smokers, testing performed to gold standards by experienced respiratory physiologists accredited to ARTP and body plethysmography assessment of lung volumes to determine TLC. There were also some limitations to the study; in retrospect with the results we have obtained it would have been useful to also assess peak cough flow (PCF) and airway resistance (RAW), as described in the results a number of inspiratory flow volume loops were excluded, it would have been interesting to perform more comprehensive bulbar function assessments and including more participants with higher Hoehn and Yahr scores would also have been very informative. As detailed in the patient information sheet, capillary blood gas sampling was attempted, this was chosen above arterial blood gas sampling to be less invasive and painful however the sampling technique was not successful in this study population and was abandoned after a number of attempts. Although a commonly used technique in neonates and paediatrics, in adults the blood would not advance successfully down the glass sampling tube and as such the analyser could not produce a result. Given the broad ranging nature of the variables studied it was decided not to apply corrections for multiple comparisons. Since the study was largely observational and exploratory, on balance it was felt that each variable considered was sufficiently unique and so no two variables were from the same family, to make correction for multiple comparisons unnecessary. This is however acknowledged as a limitation as it is important to recognise that in some cases significance may have been over estimated for this reason.

4.6 Conclusion

Reflecting back to the hypothesis that pulmonary function is impaired in PD and the aim and objective of the cross-sectional part of the study; to establish whether pulmonary function is impaired in IPD and to define the pattern of respiratory dysfunction in IPD, the hypothesis is accepted and the aim and objective have been achieved. The results of the cross-sectional study have shown a notable prevalence of obstructive spirometry, upper airways obstruction and inspiratory muscle weakness in this population. This pattern

was observed in both non-smokers and smokers or those with known obstructive lung disease. This pattern of dysfunction of the respiratory system could lead to increased morbidity and mortality. Given these significant findings, further research is warranted to assess the benefit of rehabilitation of the pulmonary system, both pharmacologically and non-pharmacologically. The effect of dopaminergic treatment on pulmonary function needs to be assessed in detail and rehabilitation, by general and specific inspiratory muscle training, warrants significant further study.

Chapter 5. Methods: Randomised control trial; the effect of an exercise intervention on pulmonary function, cardiorespiratory fitness and exercise capacity in idiopathic Parkinson's disease

The second part of the study was a RCT looking at the effect of an exercise intervention on pulmonary function, cardiorespiratory fitness and exercise capacity in IPD.

5.1 Participant recruitment

As per the cross-sectional study, participant recruitment commenced in August 2012. Individuals with IPD were recruited from the Northumbria Healthcare NHS Foundation Trust Parkinson's Service. Patients were approached in both medical and specialist nurse clinics, and given verbal information and written information sheets to take away (see appendices 9.5). The target recruitment for the study was 30. These 30 were included in the 100 in the cross-sectional study as the baseline demographics, assessments and lung function testing were the same. Patients who were willing to participate, fulfilled all inclusion criteria and with an absence of exclusion criteria, were recruited to the study and asked to sign a consent form (see appendices 9.6). The study consisted of 6 visits. At Visit 1 the participants were randomised 1:1 to a control or an intervention group. The baseline assessments took place over 3 visits during a 2 week period. The control group then received normal care for 12 weeks and the intervention group took part in a 12 week exercise intervention. After the 12 week period, all baseline assessments were repeated over the 3 visits during a 2 week period.

5.2 Inclusion criteria

Inclusion criteria for the study were:

- Idiopathic Parkinson's Disease by the UK PD Society Brain Bank Criteria.
- Hoehn and Yahr Stage I-III.
- Ability to provide written informed consent.
- Aged 18 years or over.

5.3 Exclusion criteria

Exclusion criteria for the study were:

- Other forms of Parkinsonism e.g. drug induced.
- Significant medical conditions which would preclude lung function testing.
- Significant medical conditions which would preclude exercise.
- Pregnancy.
- Recent diagnosis of a blood clot, deep vein thrombosis, pulmonary embolism or myocardial infarction.
- Unstable cardiac status, haemoptysis, pneumothorax, thoracic, abdominal or cerebral aneurysm.
- Recent eye, thoracic or abdominal surgery

5.4 Study journey, assessments, questionnaires and outcome measures

After recruitment participants were booked to attend 6 visits. Visits 1 and 4 took place in the Education Centre at North Tyneside General Hospital. Visits 2 and 5 took place in the Pulmonary Function Department at North Tyneside General Hospital. Visits 3 and 6 took place at the MoveLab, Clinical Research Facility, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP. Transport was arranged if required and travel expenses were reimbursed. Participants received no payment for participation in the study.

At visit 1, consent was confirmed and an assessment document was completed. The assessment included patient demographics, details of the patient's PD, PD medication, PD symptoms, respiratory symptoms, past medical history (PMH), family history (FH), social history (SH), exercise history, speech assessment and general examination. The Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), the Parkinson's Disease Questionnaire (PDQ-39), SCOPA-SLEEP questionnaire, Hospital Anxiety and Depression Scale (HADS), Mini Mental State Examination (MMSE), Trail Making Test and an electrocardiogram (ECG) were completed. Clinical Research Facility Standard Operating Procedures documentation was completed. Blood tests were taken for full blood count (FBC) and brain derived neurotrophic factor (BDNF). Permissions were granted for use of all rating scales. At the end of visit 1 the participants were randomised to either the control group or the intervention group. The randomisation process involved the participants blindly drawing out of a bag a piece of paper. The piece of paper had either 1 or 0 on it,

1 denoted randomisation to the intervention group, 0 denoted randomisation to the control group.

At visit 2, full pulmonary function tests were undertaken, with spirometry, lung volumes (plethysmography), diffusion and respiratory muscle strength tests Mouth Pressures and Sniff Nasal Inspiratory Pressure (SNIP).

At visit 3, cardiorespiratory fitness (aerobic capacity) was assessed with a Cardiopulmonary Exercise Test (CPET), measuring VO2peak. A Montreal Cognitive assessment (MoCA) was performed and exercise capacity was measured by the Six Minute Walk Test (6MWT).

After the first 3 visits, the control group received normal care for 12 weeks and the intervention group participated in a 12 week exercise intervention at Moor Park Healthy Living Centre, Drury Lane, North Shields, NE29 8SR. After the 12 week period, all baseline assessments were repeated in both the control and intervention groups. Visits 4, 5 and 6 followed the same format as visits 1, 2 and 3 respectively. Figure 19, below, illustrates the patient journey.

There was a minor change in the order of the assessments detailed in the patient information sheet and the patient journey above. The MoCA and 6MWT were performed at visits 3 and 6 instead of 1 and 4. The change was made in the 6MWT location due to the Clinical Research Facility having a more suitable and quiet location than the Jubilee Day Hospital for setting out the length of course required for the 6MWT. The MoCA was changed so that it was not performed on the same day as the MMSE and in addition was performed between the CPET and the 6MWT to allow the patients a period of physical rest between the two physically demanding assessments.

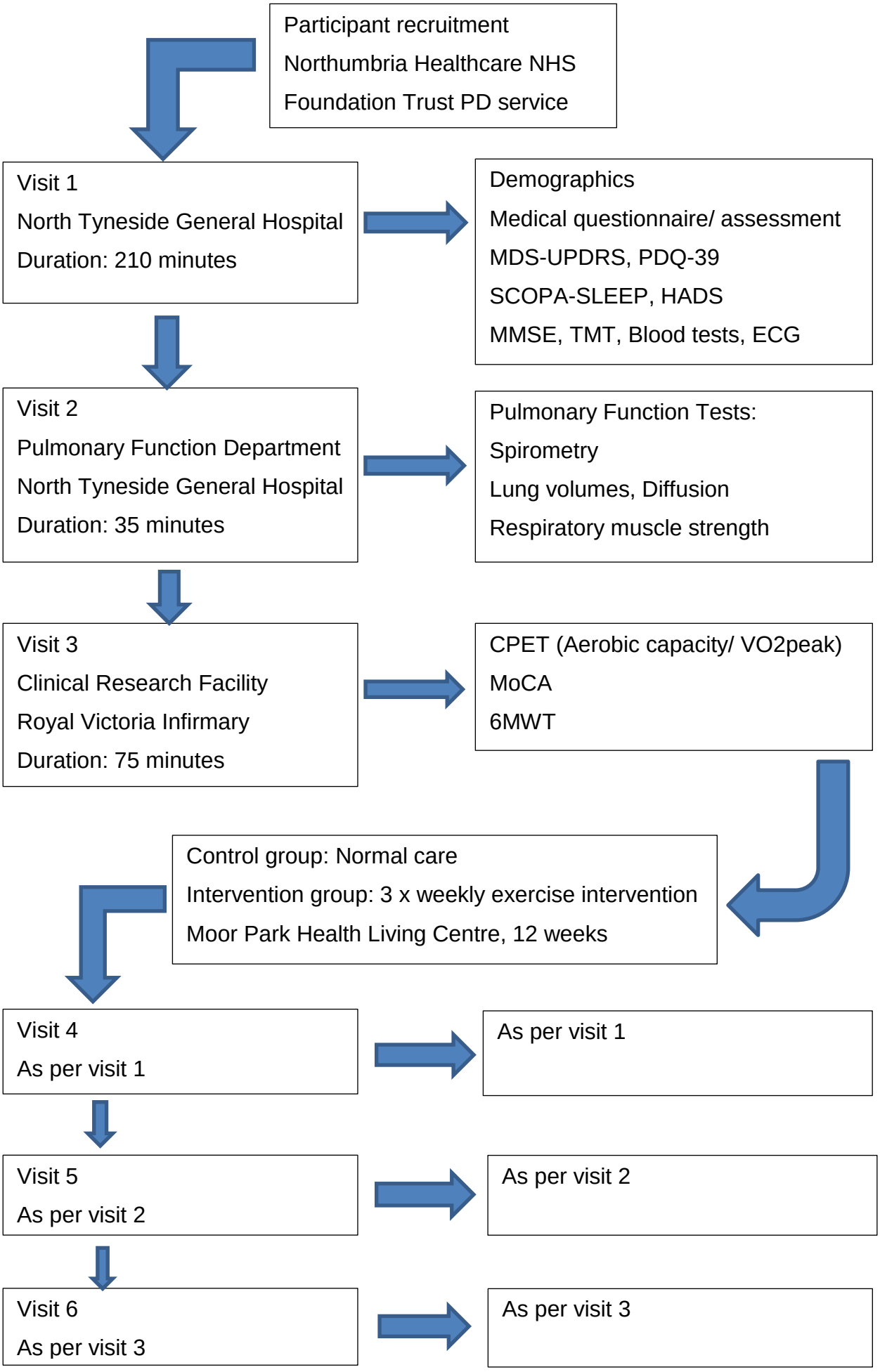

Figure 19: Randomised control trial patient journey

5.4.1 Assessment document

The assessment document (see appendices 9.7), was created by myself to ensure all relevant information was obtained, particularly focusing on history and examination findings to ensure suitability for safe pulmonary function testing, cardiopulmonary exercise and exercise capacity testing. I undertook the physical examination of all participants. The patient assessments were all completed by myself.

Each participant was allocated a unique identification number and the visit number was documented. The assessment document for the randomised control trial contained all the same questions and examinations as the cross-sectional study assessment document (see section 3.4.1), with some additional assessments. The additional assessments, as noted in the document, were related to speech and swallowing and blood tests. These additional results were analysed outwith the scope of this thesis.

5.4.2 MDS-UPDRS

As per section 3.4.2 in the cross-sectional study methods, the MDS-UPDRS was performed in all participants (see appendices 9.4). This was performed at visits 1 and 4. The MDS-UPDRS raters for the RCT were either myself or one of the Northumbria Healthcare NHS Foundation Trust Parkinson's specialist nurses, all of whom are trained in performing the rating scale.

5.4.3 PDQ-39

As per section 3.4.3 in the cross-sectional study methods, the patients completed the PDQ-39 (see appendices 9.4). This was completed at visits 1 and 4.

5.4.4 SCOPA-SLEEP

As per section 3.4.4 in the cross-sectional study methods, the patients completed the SCOPA-SLEEP scale (see appendices 9.4). This was completed at visits 1 and 4.

5.4.5 HADS

As per section 3.4.5 in the cross-sectional study methods, the patients completed the HADS (see appendices 9.4). This was completed at visits 1 and 4.

5.4.6 ECG

A 12 lead ECG was performed at visits 1 and 4, firstly to look for any abnormalities that would be a contraindication, or require review by a cardiologist prior, to cardiopulmonary exercise testing (CPET) or an exercise intervention. Abnormalities to prompt further investigation include; ST segment changes (e.g. excessive ST depression, down sloping ST depression, abnormal ST elevation), bradyarrhythmias (e.g. heartblocks, slow atrial fibrillation) and tachyarrhythmias (e.g. ventricular tachycardia, supraventricular tachycardia).
A baseline ECG and ECG monitoring is vital during CPET to differentiate normal and abnormal ECG responses to exercise. Certain ECG changes during exercise are absolute indications to terminate a CPET.
During exercise, normal ECG responses include; minor insignificant changes in P-wave morphology, increases in septal Q-wave amplitude, superimposition of the P and T-waves of successive beats, slight decreases in R-wave amplitude, increases in T-wave amplitude, depression of the J point, minimal shortening of QRS duration and rate-related shortening of the QT interval (ACSM, 2010).

5.5 Pulmonary function measurement

At visits 2 and 5, full pulmonary function tests were performed as detailed in sections 3.5, 3.5.1, 3.5.2, 3.5.3 and 3.6. All participants had spirometry, flow volume curves, lung volumes (whole body plethysmography), diffusion and respiratory muscle strength measurements.

5.6 Cardiorespiratory fitness measurement

For visits 3 and 6, participants attended the Clinical Research Facility at the Royal Victoria Infirmary for CPET. Cardiopulmonary exercise testing was completed in compliance with local standard operating procedures for exercise testing within Newcastle University and Newcastle Hospitals NHS Trust.
Aerobic capacity was assessed using a maximal progressive exercise test (ramp protocol) exercise test on an electro-magnetically controlled recumbent bicycle ergometer (Corival, Lode, Groningen, Netherlands, see figure 20). Expired gases were collected at rest for 5 minutes and continuously during the CPET. Online gas analysis was conducted using a Metalyzer 3B (Cortex, Leipzig, Germany, see figure 21). The Metalyzer works on the principle of a mixing chamber and expired gases were recorded and analysed, then averaged every 10 seconds. As per the manufacturer's guidelines, the system was

routinely calibrated for pressure, gas and volume (using a 3 litre Hans Rudolf syringe) prior to exercise tests. A 12-lead ECG (Custo, CustoMed GmbH, Ottobrunn, Germany) was continuously monitored and systolic blood pressure (SBP) and diastolic blood pressure (DBP) (Tango, SunTech Medical, Morrisville, NS, USA) were recorded twice at rest, then every 3 minutes during exercise, at VO2peak and during recovery. During the test the patient wore a Hans Rudolf facemask. The test was supervised by myself and either a physiotherapist or an exercise physiologist with certification from the American College of Sports Medicine. The physiotherapist and exercise physiologist were blinded as to whether the participants were in the control or intervention group. The test procedure was explained to the patient, they were instructed not to talk during the test but to indicate via hand gestures (thumb up or down) and by indicating their rating of perceived exertion by pointing at the Borg Rating of Perceived Exertion (RPE) scale (Borg, 1998).

As previously discussed a ramp protocol was chosen, due to this being more suitable for use in the elderly and those with PD, rather than a Bruce protocol for example which increases in steps of large increments which patients can find difficult to cope with and tire quickly. The ramp procedure CPET began with a seated rest period for 5 minutes, then a warm up period cycling at 20 watts for 3 minutes and from then on there was a progressive increase of 10 watts per minute. The participant was asked to keep the revolutions per minute (rpm) at 60 and continue until volitional exhaustion. Patients were asked to give approximately 1 minute warning before they felt they would need to end the test, to facilitate a final blood pressure measurement at the peak of exercise. The test was terminated when the patient was unable to pedal at a cadence of at least 50 rpm or they voluntarily terminated the test at exhaustion. The test was terminated by the supervisors if any of the standard criteria to terminate tests occurred; chest pain, arrhythmias, ischaemic changes on ECG or abnormal blood pressure response (>220 systolic, >115 diastolic, drop in systolic blood pressure (SBP) below resting pressure or drop in SBP with increasing workload accompanied by signs or symptoms). Peak oxygen consumption was defined as the average oxygen uptake during the last 30 seconds of exercise and expressed as ml per kg of body weight per min. Peak work rate was recorded and defined as the peak wattage when the test was terminated. Peak metabolic equivalents were calculated, by a standardised

method, as peak oxygen consumption/3.5 (Kaminsky et al., 2006). Monitoring continued during recovery.

Figure 20: The electromagnetically controlled recumbent bicycle ergometer (Corival, Lode, Groningen, Netherlands)

Figure 21: The Metalyzer (Cortex, Leipzig, Germany)

5.7 Exercise capacity, six minute walk testing

At visits 3 and 6, exercise capacity was assessed with the six minute walk test (6MWT), the distance a participant can walk in 6 minutes. The 6MWT is easier to administer, safer, better tolerated and more supremely reflects activities of daily living than other walk tests (e.g. shuttle walk test) (Enright, 2003). Validity and high test-retest reliability of the 6MWT has been found in patients with PD (Steffen and Seney, 2008). The 6MWT which is recognised for use to measure functional status, as a predictor for morbidity and mortality and as a pre-

treatment and post-treatment comparison, was performed in line with ATS guidelines (ATS, 2002).

The 6MWT was performed in a quiet flat corridor, with 30 metres marked by a tape measure and orange traffic cones. The participant was asked to walk clockwise around the cones and to cover as greater distance as possible. The participant was instructed not to jog or run and they were allowed to stop or take breaks if needed. The participant was informed when they had 3 minutes, 1 minute and 10 seconds remaining. The total distance walked (six minute walk distance (6MWD)) was recorded.

5.8 The structured exercise therapy intervention

The intervention group underwent a structured exercise programme designed to improve cardiorespiratory fitness and exercise capacity. As reviewed in section 2.4.4, there is a distinct paucity of research looking at the effect of exercise interventions on aerobic capacity or VO2peak in PD. Therefore a programme was designed by myself, in conjunction with a physiotherapist. A patient volunteer (Hoehn and Yahr III) was involved in the design and testing of the programme to ensure the programme was suitable, manageable and enjoyable for differing stages of PD including those with more advanced disease.

With aerobic capacity, or VO2max, being a function of, and thus limited by, the ability of the cardiovascular system to supply (Q_T) and/or the skeletal muscles to use (a-vO2 diff) oxygen, the programme was designed to include both aerobic and resistance exercise. Despite exercise training being a cost effective, clinically proven, primary intervention that can reduce mortality, and even delay the onset of chronic diseases, there is no consensus of the type and dose of exercise required to accrue the required benefit (Gibala et al., 2012). It was traditionally acknowledged that within each level of exercise duration, frequency, programme length or initial fitness level, the greatest improvements in VO2max occurred when the participants exercised at higher intensities (e.g. from 90 to 100% of V̇O2max) with maximal gains at a frequency of 4 times per week and exercise duration of 35-45 minutes. Lower intensities still produced effective changes and reduced injury risk. As fitness improved, the change in VO2max decreased regardless of the intensity, frequency or duration of exercise, or to put it another way, the more unfit had the most to gain (Wenger and Bell, 1986). In recent years there has been a growing interest in high

intensity interval training (HIT) which is considered able to serve as an effective alternative to traditional endurance-based training and although less well studied, low-volume HIT is acknowledged to stimulate physiological remodelling comparable to moderate intensity continuous training (Gibala et al., 2012). Thus no consensus remains on exercise programmes in health and disease.

With the paucity of research in this area in PD, the exercise programme was designed to improve cardiorespiratory fitness, be manageable and safe for those with PD and use simple readily available equipment and thus make the study reproducible. The 12 week, 3 times per week, exercise intervention took place at Moor Park Healthy Living Centre (HLC), which is a gym with specially trained staff and resuscitation equipment that accepts public and NHS referrals. The HLC is a site for cardiac and pulmonary rehabilitation and all staff are trained to British Association of Cardiac Rehabilitation level 4 and GP referral qualification level 3. The participants were exercised in groups of 5, to facilitate a circuit training approach and the appropriate level of supervision (at least 2 qualified staff per session). The HLC was closed to the public and other users during the exercise intervention. Pulse and oxygen saturations were measured before and after each session and heart rate monitors (RS400, Polar, Finland) were worn throughout. All sessions were in the afternoons and participants were exercised in the on state.

The participants started and finished each session with a gentle 10 minute warm up and cool down respectively, including stretches. Each participant commenced at an aerobic station and moved around the 12 stations in a circuit. The stations alternated between aerobic and resistance. The aerobic stations were 4 minutes in duration and the resistance stations were 2 minutes in duration. Over the course of the 12 weeks the aerobic stations were increased to 5 minutes in duration as tolerated and time was allowed within the protocol for movement between equipment. To increase intensity over the 12 weeks, on relevant stations and within individual capabilities, speed, level, incline, step height and rating of perceived exertion were increased and weights and bands were added. Thus at the start of the study, aerobic stations comprised 6 x 4 minutes (24 minutes) and resistance stations comprised 6 x 2 minutes (12 minutes) totalling 36 minutes, with the addition of the warm up and cool down. This allowed for an increase on the aerobic stations of 1 minute per station later in the programme thus a total of 42 minutes and to allow for moving between

stations each session was approximately 45 minutes plus warm up and cool down. Table 15, below, summarises the exercise intervention.

Station	Exercise	Progression
1. Aerobic 4 mins	Treadmill	• Increase speed • Increase incline • Increase to 5 mins
2. Resistance 2 mins	Upright rowing	• Add weights/band
3. Aerobic 4 mins	Sit to stand From chair	• Use a chair without arms • Increase to 5 mins
4. Resistance 2 mins	Lateral raises	• Add a band/weights
5. Aerobic 4 mins	Marching/ Step ups	• Add a step • Increase step height • Increase speed • Increase to 5 mins
6. Resistance 2 mins	Triceps kick backs	• Add weight
7. Aerobic 4 mins	Hand bike	• Increase Speed • Increase level • Increase to 5 mins
8. Resistance 2 mins	Rotator cuff	• Add a band/weights • Increase band difficulty
9. Aerobic 4 mins	Recumbent Bike	• Increase speed • Increase level • Increase to 5 mins
10. Resistance 2 mins	Bicep curl	• Add weights
11. Aerobic 4 mins	Boxing	• Increase exertion • Increase to 5 mins
12. Resistance 2 mins	Chest stretch at 90 degrees	• Add band/ use wall

Table 15: The exercise intervention

At the end of each exercise session, in addition to the cool down, pulse and oxygen saturations check, all participants were observed for recovery prior to leaving the HLC.

5.9 Follow up 12 week assessments

All assessments were repeated at 12 weeks, for the control group after normal care and for the intervention group after the exercise intervention. Visits 1, 2 and 3 corresponded to visits 4, 5 and 6 respectively for repeat testing. After visit 6, the control group were offered the opportunity to participate in a 12 week exercise programme at Moor Park Healthy Living Centre (HLC), if they wished to do so.

5.10 Sample size calculations

Based on previous stroke data (unpublished data and personal communication from a study based at the Clinical Research Facility) and the reported statistically significant improvement in VO2max in the Bergen et al 2002 study of 5ml/kg/min or 26%, assuming a clinically significant improvement in VO2max to be 5 and assuming the standard deviation for the change in scores from baseline to post-intervention in VO2max to be no greater than 4 and setting alpha =0.05 and power at 0.9 and using a t-test for 2 related samples gives desired sample size of 6.7, rounding this up to 7 to achieve statistical significance (Bergen et al., 2002).

Increase in 6MWT is likely to be the outcome of most relevance to the patients. Based on the work of Koseoglu et al who observed a mean increase in 6MWT distance of 108.1 (SD 31.954), setting alpha =0.05 and power at 80% and using a t-test for 2 related samples gives a sample size of 5 to achieve statistical significance (Koseoglu et al., 1997). Thus a RCT sample of 30 (15 intervention, 15 control) allows for significant dropout to still achieve statistical significance in primary outcomes. A larger sample size was chosen to endeavour to have enough participants to achieve statistical significance as the increase in 6MWT observed in the Koseoglu study was large however their sample size was small and it was the only prior study that focused on PD, lung function and 6MWT. Quoted values for minimal clinically significant difference in 6MWT vary widely between different chronic diseases, in older adults small meaningful change of 20 m and substantial change of 50 m for 6MWT has been quoted (Perera et al., 2006).

Chapter 6. Results: Randomised control trial; The effect of an exercise intervention on pulmonary function, cardiorespiratory fitness and exercise capacity in idiopathic Parkinson's disease

With the distinction between the 2 sections of the study, this chapter concerns the results, discussion and conclusion of the RCT. Having been approached by the Northumbria PD team, 32 patients volunteered to take part in the RCT arm of the study. These 32 were randomised 1:1 intervention to control thus 16 in each group. A total of 27 participants completed the RCT. Two participants from the control group failed to complete the study. The first due to inability to perform the CPET, he was unable to pedal at a cadence of 50 rpm (this seemed to be due to failure to understand the instructions despite repeated attempts), thus the exercise test was abandoned. The second participant from the control group who failed to complete the study was admitted to hospital during the 12 week normal care period, with an unrelated illness, but due to her ongoing investigations she was excluded from follow up testing. Thus of the 2 participants who discontinued the study from the control group both had participation terminated by the investigator. Thus 14 participants completed the control group. In the intervention group 13 participants completed the study, thus 3 failed to complete. The first participant to withdraw underwent all baseline testing then subsequently declined the exercise intervention as she was concerned she would struggle to complete. The second and third withdrawals occurred during the intervention (1 participant's relative became unwell and he withdrew to assume a carer's role and 1 participant had a viral illness and decided to withdraw).Thus of the 3 who discontinued the study in the intervention group all 3 were withdrawals by the participants. Figure 22, below summarises the recruitment, drop out and completion.

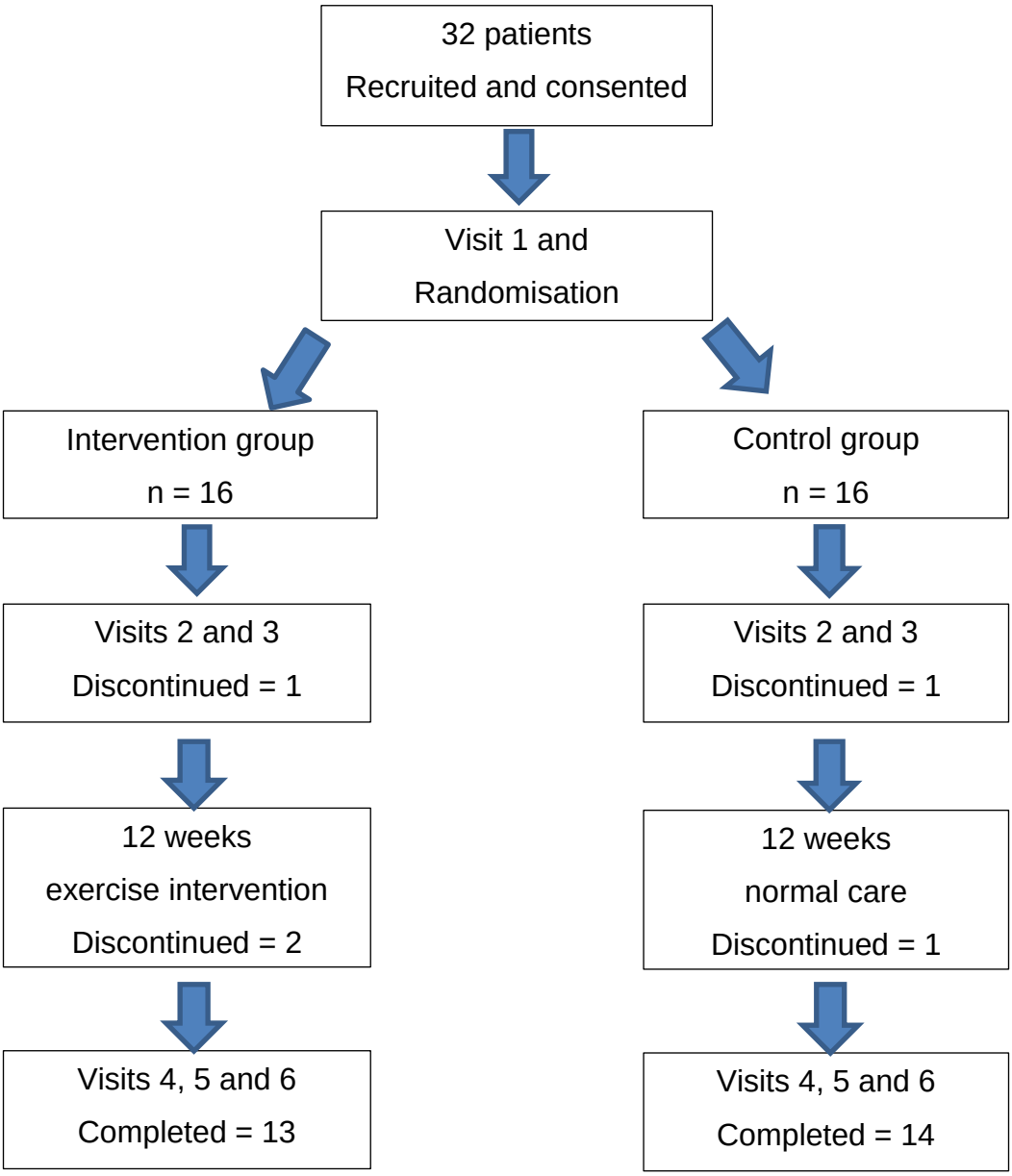

Figure 22: Randomised control trial; recruitment, drop out and completion

The exercise intervention comprised 36 sessions. The 13 participants who completed the exercise intervention had a median session attendance of 32, Interquartile Range (IQR) 28 – 35, range 27 – 36. Thus all participants who completed the intervention attended at least 75% of structured exercise sessions.

Results were inputted by a research assistant and second checked by myself. There was no missing data in the RCT. The data was not normally distributed, on review of histograms, as such medians and interquartile ranges are quoted and non-parametric tests (Wilcoxon signed-rank) were used to analyse the paired data. Visual inspection of the data distribution using histograms was

used for assessing normality, as in chapter 4 in cases where there was any discrepancy in the distribution on visual inspection the statistical Kolmogorov-Smirnov test of normality was used. Alpha was set at 0.05. The study produced interesting results in two distinct ways; the effect of a 12 week exercise intervention and the physiological response to an acute episode of maximal exercise in PD. The following tables detail the group median and interquartile ranges for the variables pre and post the exercise intervention in the control and intervention groups. The final 2 columns of the tables detail the median change from baseline scores, and interquartile ranges, in the individuals in the control group and intervention group with the associated z scores and p scores from the Wilcoxon signed-rank test results.

Table 16 below, details the demographics of the control and intervention groups pre and post the exercise intervention. The median ages of the control and intervention groups were comparable at 67.5 and 68 years respectively, while the duration of disease since diagnosis was lower in the intervention group than the control group. Both before and after the intervention, the group median BMI and levodopa equivalent dose were lower in the intervention group than the control group. In either group BMI was not significantly changed after the 12 week exercise intervention or 12 weeks of normal care. As described in section 4.1 of the cross-sectional study, levodopa equivalent dose (LED) was calculated using the conversion formulae developed by Tomlinson et al (Tomlinson et al., 2010).

The UPDRS section scores and Hoehn and Yahr scores pre and post the intervention are reported in table 17. It was notable that both before and after, the control group subjectively reported their parkinsonian symptoms, as reported in UPDRS sections 1 and 2, to be worse than those of the intervention group noting also that the control group had longer median disease duration than the intervention group. At baseline the UPDRS 3 objective median score was higher in the intervention group. Statistically significant changes from baseline after the 12 weeks of exercise or normal care were only seen in the intervention group as improvements in UPDRS 1 and 2 section scores. Although UPDRS section 3 in the intervention group changed from baseline by a median improvement of 2 points, this did not reach statistical significance.

	Control Baseline N=14 Median (IQR)	Intervention Baseline N=13 Median (IQR)	Control Follow up N=14 Median (IQR)	Intervention Follow up N=13 Median (IQR)	Control change from baseline N=14 Median (IQR) Wilcoxon signed-rank test	Intervention change from baseline N=13 Median (IQR) Wilcoxon signed-rank test
Age (years)	67.5 (57.3 – 69.8)	68.0 (65.5 – 75.5)	67.5 (58.3 – 69.8)	68.0 (65.5 – 75.5)		
BMI (kg/m^2)	26.7 (24.3 – 29.3)	24.5 (22.8 – 27.7)	26.9 (24.6 – 29.3)	24.6 (22.7 – 27.7)	0.1 (-0.2 – 0.4) Z = -0.707 P = 0.479	0.1 (-0.3 – 0.3) Z = -0.395 P = 0.693
Disease duration (months)	95.5 (15.0 – 120.3)	33.0 (21.0 – 71.5)	98.5 (17.3 – 123.3)	36.0 (25.0 – 76.5)		
Levodopa equivalent dose (mg)	520.0 (265.0 – 839.3)	400.0 (230.0 – 620.0)	540.0 (375.0 – 975.0)	400.0 (230.0 – 490.0)	0.0 (0.0 – 112.5) Z = -2.197 P = 0.028	0.0 (0.0 – 25.0) Z = -0.365 P = 0.715

Table 16: Demographics of the control and intervention groups pre and post the exercise intervention

	Control Baseline N=14 Median (IQR)	Intervention Baseline N=13 Median (IQR)	Control Follow up N=14 Median (IQR)	Intervention Follow up N=13 Median (IQR)	Control change from baseline N=14 Median (IQR) Wilcoxon signed-rank test	Intervention change from baseline N=13 Median (IQR) Wilcoxon signed-rank test
UPDRS Part 1	10.5 (4.0 – 14.0)	5.0 (3.5 – 10.0)	8.0 (2.8 – 13.5)	3.0 (2.0 – 6.0)	-1.0 (-2.5 – 1.3) Z = -0.990, P = 0.322	-1.0 (-1.0 - 3.0) Z = -2.966, P = 0.003
UPDRS Part 2	11.0 (6.0 – 14.0)	6.0 (3.5 – 10.0)	13.0 (7.8 – 14.0)	4.0 (2.0 – 9.5)	1.5 (-0.3 – 2.3) Z = -1.870, P = 0.062	-2.0 (-4.0 – 0.0) Z = -2.288, P = 0.022
UPDRS Part 3	20.5 (12.8 – 34.8)	23.0 (17.0 – 31.0)	22.5 (18.3 – 38.3)	21.0 (14.5 – 29.5)	4.0 (-4.0 – 7.3) Z = -1.242, P = 0.214	-2.0 (-6.0 – 3.5) Z = -0.550, P = 0.582
UPDRS Part 4	0.0 (0.0 – 3.8)	0.0 (0.0 – 3.5)	0.0 (0.0 – 3.3)	0.0 (0.0 – 1.0)	0.0 (-3.5 – 2.0) Z = -0.635, P = 0.526	0.0 (-3.0 – 0.0) Z = -1.838, P = 0.066
Hoehn and Yahr	2.0 (2.0 – 2.0)	2.0 (2.0 – 2.0)	2.0 (2.0 – 2.0)	2.0 (2.0 – 2.0)	0.0 (0.0 – 1.0) Z = -2.000, P = 0.046	0.0 (0.0 – 0.0) Z = 0.000, P = 1.000

Table 17: UPDRS and Hoehn and Yahr scores pre and post intervention

Resting cardiovascular parameters and peak heart rate pre and post the intervention or normal care are reported in table 18. Cardiorespiratory fitness and exercise capacity pre and post intervention or normal care are reported in table 19. Both the control group and the intervention group had median normal resting systolic and diastolic blood pressure at baseline and follow up, with no statistically significant changes in these parameters. At follow up, resting heart rate showed a statistically significant drop in both the control and the intervention groups. At follow up, peak heart rate achieved during the maximal cardiopulmonary exercise test also fell in both the control and intervention groups.

The primary outcomes in the RCT were those of cardiorespiratory fitness (aerobic capacity), as measured by VO2peak and exercise capacity, as measured by six minute walk distance (6MWD). In the control group there were no significant changes after 12 weeks in anaerobic threshold at percent of VO2max predicted, VO2peak, peak metabolic equivalents, peak work rate and 6MWD. In contrast, in the intervention group after 12 weeks structured exercise therapy statistically significant improvements were seen in all these outcomes. In the intervention group the median individual change from baseline was 9.7% for anaerobic threshold at percent of VO2max predicted, 2.0ml/kg/min for VO2peak, 0.7METS for peak metabolic equivalents, 8.0watts for peak work rate and 39.8m for 6MWD. The relevance of anaerobic threshold at percentage of VO2max predicted is that the better an individual’s cardiorespiratory fitness is, the closer the anaerobic threshold should be to the VO2max. In our study population this anaerobic threshold at percent of VO2max predicted improved by almost 10%. Figure 23 illustrates the effects of the exercise intervention or normal care on median change from baseline for anaerobic threshold percentage of VO2max predicted. Figure 24 illustrates the effects of the exercise intervention or normal care on median change from baseline for VO2peak, thus cardiorespiratory fitness.

	Control Baseline N=14 Median (IQR)	Intervention Baseline N=13 Median (IQR)	Control Follow up N=14 Median (IQR)	Intervention Follow up N=13 Median (IQR)	Control change from baseline N=14 Median (IQR) Wilcoxon signed-rank test	Intervention change from baseline N=13 Median (IQR) Wilcoxon signed-rank test
Resting heart rate (bpm)	73.0 (67.0 – 82.8)	71.0 (65.0 – 82.5)	69.0 (64.0 – 76.0)	68.0 (61.0 – 76.5)	-3.5 (-8.5, -0.8) Z = -2.909, P = 0.004	-3.0 (-8.5, -1.0) Z = -2.140, P = 0.032
Resting systolic BP (mmHg)	129.5 (117.8 – 149.3)	132.0 (122.5 – 137.0)	127.0 (120.5 – 133.5)	128.0 (115.5 – 137.5)	1.5 (-21.5 – 9.8) Z = -0.283, P = 0.777	0.0 (-19.5 – 7.5) Z = -0.785, P = 0.432
Resting diastolic BP (mmHg)	76.5 (72.0 – 92.0)	78.0 (72.0 – 86.0)	83.0 (78.8 – 89.8)	83.0 (71.5 – 85.5)	4.0 (-5.5 – 9.3) Z = -1.069, P = 0.285	2.0 (-4.0 – 7.0) Z = -0.735, P = 0.462
Peak heart rate (bpm)	122.0 (113.0 – 128.8)	124.0 (109.0 – 129.5)	116.5 (107.8 – 129.3)	120.0 (103.5 – 128.0)	-2.0 (-7.5 – 0.3) Z = -2.069, P = 0.039	-5.0 (-6.5 – 3.0) Z = -1.472, P = 0.141

Table 18: Resting cardiovascular parameters and peak heart rate pre and post intervention

	Control Baseline N=14 Median (IQR)	Intervention Baseline N=13 Median (IQR)	Control Follow up N=14 Median (IQR)	Intervention Follow up N=13 Median (IQR)	Control change from baseline N=14 Median (IQR) Wilcoxon signed-rank test	Intervention change from baseline N=13 Median (IQR) Wilcoxon signed-rank test
Anaerobic threshold at %VO2peak	60.8 (41.2 – 76.2)	42.9 (32.7 – 57.5)	58.9 (50.5 – 72.3)	50.0 (42.5 – 64.5)	-3.9 (-8.6 – 13.0) Z = -0.157, P = 0.875	9.7 (3.0 – 14.3) Z = -2.622, P = 0.009
VO2peak (ml/kg/min)	20.0 (17.3 – 23.0)	16.0 (15.0 – 23.0)	20.0 (16.5 – 23.3)	20.0 (17.5 – 25.5)	0.0 (-1.0 – 1.0) Z = -0.431, P = 0.667	2.0 (0.5 – 4.5) Z = -2.602, P = 0.009
METS	5.7 (4.8 – 6.7)	4.5 (4.2 – 6.5)	5.7 (4.7 – 6.6)	5.7 (5.0 – 7.2)	0.0 (-0.2 – 0.1) Z = -0.317, P = 0.751	0.7 (0.2 – 1.3) Z = -2.520, P = 0.012
Peak work rate (watts)	99.0 (82.8 – 117.0)	96.0 (80.5 – 138.0)	91.0 (80.8 – 126.5)	122.0 (79.5 – 154.5)	4.5 (-13.0 – 10.8) Z = -0.126, P = 0.900	8.0 (1.0 – 16.0) Z = -2.201, P = 0.028
6MWD (m)	532.7 (413.3 – 565.1)	461.1 (431.3 – 555.8)	505.0 (417.7 – 570.4)	496.8 (463.6 – 623.8)	3.2 (-30.6 – 32.1) Z = -0.220, P = 0.826	39.8 (13.0 – 58.9) Z= -3.180, P = 0.001

Table 19: Cardiorespiratory fitness and exercise capacity pre and post intervention

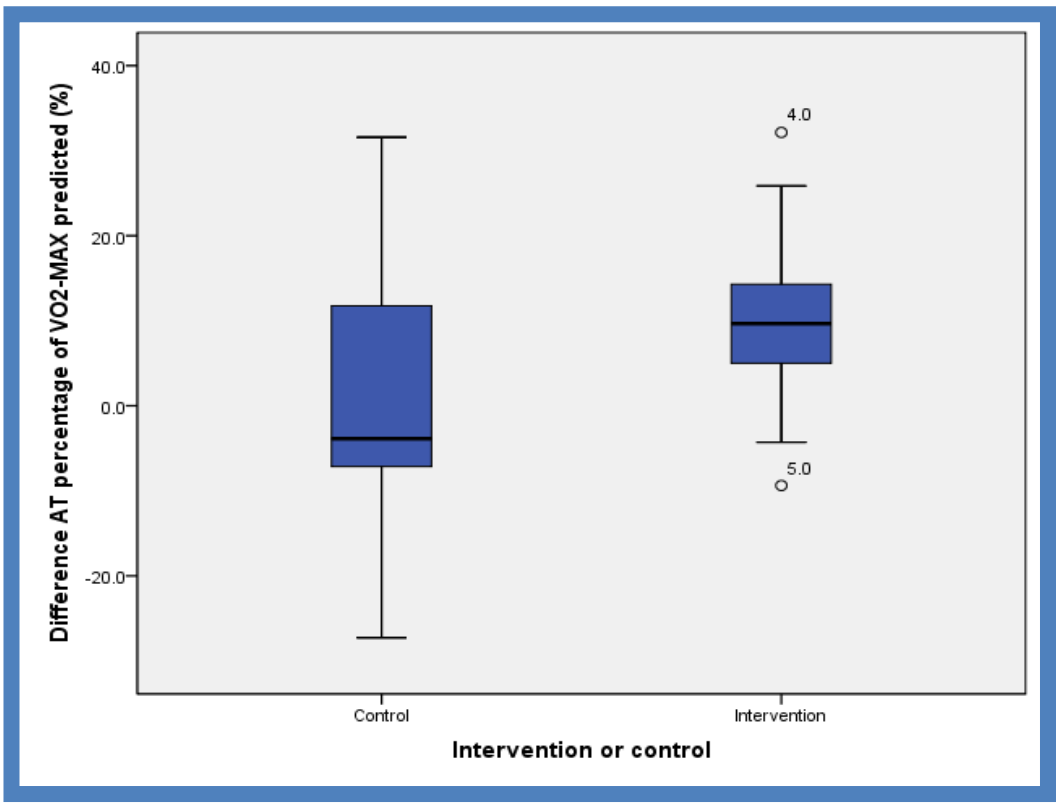

Figure 23: Effects of exercise intervention on median change from baseline anaerobic threshold percentage of VO2max predicted

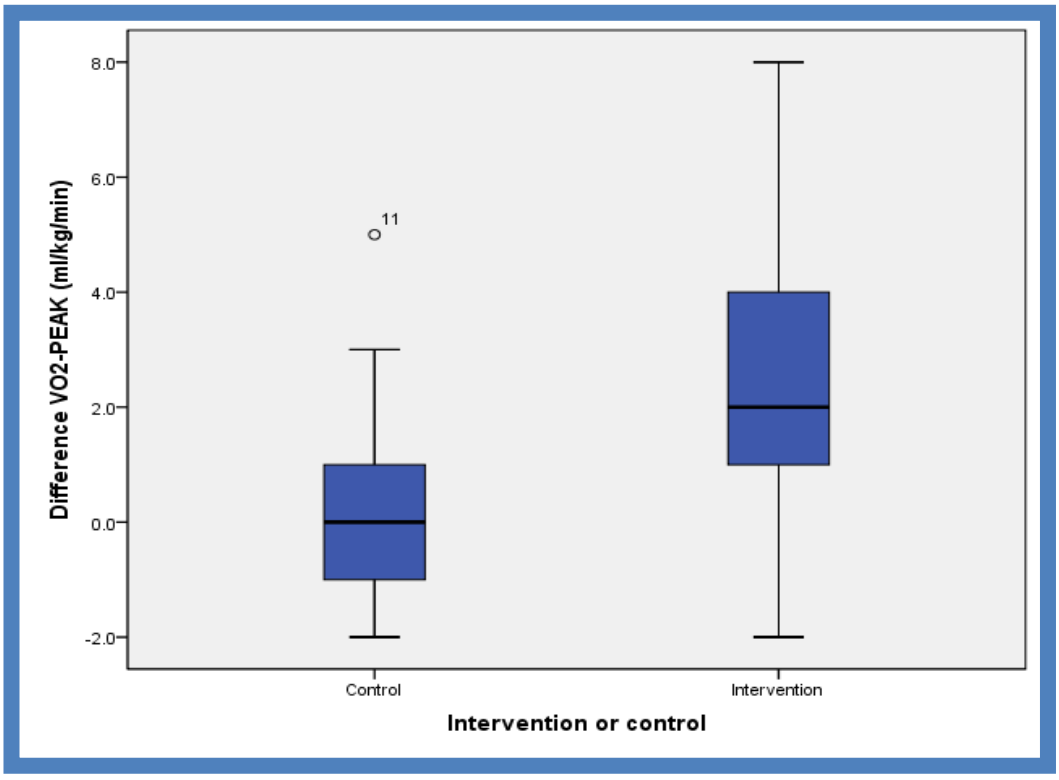

Figure 24: Effects of exercise intervention on median change from baseline on VO2peak, cardiorespiratory fitness

Having reported the objective outcomes of aerobic capacity and exercise capacity it is important to consider the effects of the exercise intervention on self-rated reports of quality of life, sleep, anxiety and depression. Table 20 below, reports the effect of the exercise intervention or 12 weeks normal care on the PDQ 39 single index, SCOPA-SLEEP scores and the Hospital Anxiety and Depression Scale (HADS) scores. Following the exercise intervention in the intervention group or 12 weeks normal care in the control group, statistically significant results were only seen in the intervention group and these were as improvements in the PDQ 39 single index, SCOPA C, SCOPA D, HADS A and HADS D scores. The median change from baseline in the intervention group for these parameters was -2.2 for the PDQ 39 single index, -1.0 for overall quality of night time sleep, -1.0 for sleepiness in the daytime and evenings, -1.0 for anxiety and -1.0 for depression. For the PDQ-39, SCOPA-SLEEP and HADS, lower score reflect an improvement in symptoms.

Table 21 below, reports the pulmonary function and respiratory muscle strength test results pre and post either the exercise intervention or 12 weeks normal care. As noted in the cross-sectional study of pulmonary function, in both the control and intervention groups, the inspiratory muscle strength tests (MIP and SNIP) were worse than the expiratory muscle strength test (MEP) and in addition to this, SNIP was again worse than MIP. The pulmonary function and respiratory muscle strength tests focused on in the RCT were predominantly the effort dependent variables to look at the effect of exercise. In both the control and the intervention groups, no statistically significant changes were seen in percent predicted values of FEV1, FVC, PEF, MEP, MIP and SNIP. Of note the median FEV1/FVC of both the control and intervention groups, pre and post, exceeded 70%. Whilst there was a trend in the intervention group of an improvement post exercise intervention in percent predicted MIP, this did not reach statistical significance and was also not reflected in the SNIP results.

	Control Baseline N=14 Median (IQR)	Intervention Baseline N=13 Median (IQR)	Control Follow up N=14 Median (IQR)	Intervention Follow up N=13 Median (IQR)	Control change from baseline N=14 Median (IQR) Wilcoxon signed-rank test	Intervention change from baseline N=13 Median (IQR) Wilcoxon signed-rank test
PDQ 39 single index	22.1 (9.2 – 30.6)	9.4 (6.2 – 17.0)	17.1 (8.2 – 30.4)	6.3 (3.3 – 12.6)	-0.7 (-6.6 – 1.0) Z = -1.224, P = 0.221	-2.2 (-4.5 – 0.1) Z = -2.201, P = 0.028
SCOPA B	4.5 (1.8 – 8.3)	4.0 (2.5 – 6.0)	5.5 (0.75 – 8.3)	3.0 (1.0 – 4.5)	0.0 (-1.25 – 1.25) Z = -0.103, P = 0.918	-1.0 (-3.5 – 0.0) Z = -1.586, P = 0.113
SCOPA C	3.5 (1.0 – 5.0)	3.0 (2.0 – 4.0)	3.0 (1.0 – 4.0)	2.0 (1.5 – 3.5)	0.0 (-1.0 – 0.0) Z = -1.186, P = 0.236	-1.0 (-1.0 – 0.0) Z = -2.636, P = 0.008
SCOPA D	3.5 (2.8 – 5.5)	4.0 (1.5 – 6.0)	4.0 (1.0 – 7.0)	2.0 (0.5 – 3.5)	0.0 (-1.3 – 2.3) Z = -0.381, P = 0.704	-1.0 (-2.5 – 0.0) Z = -2.446, P = 0.014
HADS A	5.0 (2.8 – 8.3)	3.0 (1.5 – 6.0)	4.0 (3.3 – 7.3)	1.0 (0.0 – 3.5)	-1.0 (-2.0 – 0.0) Z = -1.085, P = 0.278	-1.0 (-2.5 – 0.0) Z = -2.155, P = 0.031
HADS D	6.0 (3.0 – 8.3)	4.0 (2.0 – 5.0)	5.5 (2.8 – 9.3)	2.0 (1.0 – 2.5)	0.5 (-1.3 – 1.0) Z = -0.072, P = 0.943	-1.0 (-3.0, -1.0) Z = -2.969, P = 0.003

Table 20: PDQ 39 single index, SCOPA-SLEEP and HADS scores pre and post intervention

	Control Baseline N=14 Median (IQR)	Intervention Baseline N=13 Median (IQR)	Control Follow up N=14 Median (IQR)	Intervention Follow up N=13 Median (IQR)	Control change from baseline N=14 Median (IQR) Wilcoxon signed-rank test	Intervention change from baseline N=13 Median (IQR) Wilcoxon signed-rank test
FEV1 %predicted	110.0 (99.5 – 117.0)	118.0 (97.0 – 125.0)	106.5 (97.8 – 117.5)	115.0 (99.0 – 128.0)	-1.0 (-4.5 – 2.3) Z = -1.026, P = 0.305	0.0 (-2.0 – 6.0) Z = -1.175, P = 0.240
FVC %predicted	122.5 (110.0 – 134.0)	125.0 (107.0 – 130.5)	123.5 (115.3 – 127.0)	126.0 (107.0 – 129.5)	1.5 (-6.3 – 5.3) Z = -0.140, P = 0.889	-1.0 (-10.0 – 3.0) Z = -0.890, P = 0.373
PEF %predicted	102.0 (87.0 – 111.0)	110.0 (92.5 – 125.5)	105.5 (94.0 – 112.5)	112.0 (100.0 – 125.0)	1.0 (-1.5 – 12.3) Z = -1.601, P = 0.109	2.0 (-3.0 – 9.5) Z = -1.295, P = 0.195
MEP %predicted	93.7 (78.8 – 113.9)	94.4 (77.8 – 104.6)	98.4 (84.6 – 104.9)	90.8 (64.5 – 101.8)	3.2 (-16.1 – 20.6) Z = -0.345, P = 0.730	-1.1 (-25.2 – 5.5) Z = -0.943, P = 0.345
MIP %predicted	81.9 (74.0 – 95.0)	81.3 (50.4 – 129.5)	92.4 (69.8 – 111.5)	93.6 (71.8 – 116.5)	5.8 (-4.4 – 18.8) Z = -0.973, P = 0.331	15.2 (-5.5 – 24.5) Z = -1.642, P = 0.101
SNIP %predicted	61.6 (34.4 – 97.9)	68.6 (37.3 – 91.3)	62.5 (43.5 – 90.1)	76.6 (59.3 – 87.0)	7.8 (-7.9 – 15.1) Z = -1.099, P = 0.272	2.8 (-19.4 – 31.5) Z = -0.664, P = 0.507

Table 21: Pulmonary function and respiratory muscle strength pre and post intervention

As noted at the beginning of this results section, the study produced interesting results in two distinct ways; the effect of a 12 week exercise intervention and the physiological response to an acute episode of maximal exercise in PD. The results above focused on the effect of a 12 week exercise intervention, the table below, table 22, reports the effect of an acute episode of maximal exertion in the form of the cardiopulmonary exercise test.

	Control Baseline N=14 Median (IQR)	Intervention Baseline N=13 Median (IQR)	Control Follow up N=14 Median (IQR)	Intervention Follow up N=13 Median (IQR)
Peak heart rate (bpm)	122.00 (113.00 - 128.75)	124.00 (109.00 - 129.5)	116.50 (107.75 129.25)	120.00 (103.50 - 128.00)
Heart rate %predicted	75.30 (67.38 - 82.35)	76.69 (67.59 - 81.22)	75.29 (64.75 - 82.57)	75.90 (68.05 - 80.06)

Table 22: Heart rate response to cardiopulmonary exercise test

As reported also in table 18, it is noted that in both the control and intervention groups, pre and post the intervention or normal care 12 weeks, the peak heart rate achieved during the maximal cardiopulmonary exercise tests was significantly lower than the predicted value. At baseline and follow up, each group median peak heart rate was below 77% predicted. This result was not reflected in the median VO2peaks achieved, at baseline and follow up, in each group which were equal to or exceeded 90% predicted. The only heart rate limiting medication that any participant was taking was a beta blocker. Two participants in the intervention group and two in the control group were prescribed beta blockers. Allowing for this, when the heart rate data was analysed not including those on beta blockers, there was not a significant difference in the findings and the peak heart rates achieved remained significantly lower than would be predicted. There is considerable debate on the most appropriate predication equation for maximal heart rate with the most well recognised being 220-age, however a vast number of other prediction equations exist (Robergs and Landwher, 2002). Using 3 different maximal heart rate

prediction equations continued to show the peak heart rate achieved in our population remained well below the expected value.
The effect of a structured exercise intervention and the physiological response to an acute episode of maximal exercise in PD warrant further detailed discussion.

6.1.1 Discussion

The RCT primarily looked at the effect of a structured exercise intervention on cardiorespiratory fitness as defined by VO2peak, but also looked at the effect of an exercise intervention on markers of cardiovascular health, exercise capacity (6MWD), pulmonary function, respiratory muscle strength, parkinsonian symptoms, Parkinson's disease stage, quality of life, sleep, anxiety and depression. The above looked at the effect of a period of training on these outcomes, and the study also had the benefit of assessing a cardiorespiratory response to an acute episode of maximal exercise. With scope of the study covering all these areas, the discussion will be divided accordingly.
Before discussing the effect of the exercise intervention, the differences between the control group and intervention group at baseline warrant further discussion. The median age between the groups was comparable at 67.5 years in the control group and 68.0 years in the intervention group however the control group had a longer disease duration (95.5 months versus 33.0 months) and higher levodopa equivalent dose (520.0mg versus 400.0mg) than the intervention group. With PD being a progressive disease it is unsurprising that those with a longer disease duration required higher doses of medication. In the patient scored subjective rating scales of UPDRS part 1, UPDRS part 2, PDQ-39 single index and HADS A and HADS D the control group rated themselves worse than the intervention group (UPDRS part 1 10.5 versus 5.0, UPDRS part 2 11.0 versus 6.0, PDQ-39 single index 22.1 versus 9.4, HADS A 5.0 versus 3.0 and HADS D 6.0 versus 4.0). Again this may be expected that those with the longer disease duration have a greater impact of their PD on their physical abilities, quality of life, anxiety and depression. Interestingly on the objective ratings of disease stage (Hoehn and Yahr), UPDRS 3, cardiorespiratory fitness (VO2peak) and exercise capacity (6MWD) this trend was not continued. Both groups had the same median Hoehn and Yahr score of 2.0 and across the other outcome measures the control group performed better than the intervention

group (UPDRS 3 20.5 versus 23.0, VO2peak 20.0ml/kg/min versus 16.0ml/kg/min and 6MWD 532.7m versus 461.1m). This was a very interesting finding as it may be expected that those with longer disease duration would have more advanced disease stage, worse UPDRS motor scores, worse cardiorespiratory fitness and worse exercise capacity however this was not the case. A possible reason for this difference in objective and subjective findings may be the effect of having a progressive neurodegenerative disorder for a longer period of time affects psychology and perceptions of health faster and more profoundly than it affects ability.

6.1.2 Discussion: Effect of an exercise intervention on cardiorespiratory fitness and exercise capacity

In the intervention group only, there were significant changes after 12 weeks in anaerobic threshold at percent of VO2max predicted, VO2peak, peak metabolic equivalents, peak work rate and 6MWD. In the intervention group the median individual change from baseline was 9.7% for anaerobic threshold at percent of VO2max predicted, 2.0ml/kg/min for VO2peak, 0.7METS for peak metabolic equivalents, 8.0watts for peak work rate and 39.8m for 6MWD. The improvement seen in aerobic capacity as measured by VO2peak was comparable to that reported in healthy sedentary adults following a period of structured exercise of 10 – 30% improvement (Samitz and Bachl, 1991). Thus it would appear that individuals with PD can enjoy the same level of benefits in terms of aerobic capacity with a period of exercise training as normal, healthy individuals. As would be expected with an increase in aerobic capacity, and as such fitness, the anaerobic threshold moved closer to the VO2peak, the peak metabolic equivalent improved, the peak work rate improved and the 6MWD distance improved. With the associated improvement in 6MWD distance, considering the availability of equipment for cardiopulmonary exercise testing and the skills of the technicians required to undertake CPET tests, 6MWD could be considered for use as a surrogate marker for aerobic capacity if the gold standard is not available. While predominantly discussing VO2peak, it is important to mention the concept of metabolic equivalents or METS. The MET concept provides a simple technique to describe functional capacity and with known energy expenditure values, in METS and watt units, for household task and recreational activities allows simple visual imagery of energy expenditure

(Jette et al., 1990). The increase in METS observed in the intervention group could represent the increased ability of an individual to be able to perform heavy household chores rather than light household chores.

As discussed in section 2.4, after endurance training, SV is increased at rest and during submaximal and maximal exercise, whilst HR is decreased at rest and during submaximal exercise and unchanged at maximal work rates. Training increases plasma volume and end diastolic volume and results in more elastic recoil. Long term responses also include hypertrophy of cardiac muscle fibres and reduction in blood pressure. Interestingly both the control and the intervention group showed a statistically significant reduction in resting heart rate after the 12 week period of normal care or the exercise intervention respectively, thus this effect cannot be concluded to be in response to training. In both groups there was no statistically significant change in resting systolic or diastolic blood pressure in either group. There are potential reasons why these abnormal cardiovascular responses to a period of training have occurred, despite the observed increase in aerobic capacity, VO2peak. It is reported that the dysautonomia in Parkinson's disease involves neurocardiological abnormalities with postganglionic sympathetic noradrenergic lesions which may be responsible for this abnormal cardiac response to training (Goldstein, 2003). As previously discussed Cardiac output (QT) is the volume of blood the heart pumps out in one minute and is the product of the stroke volume (SV) ,which is the amount of blood pumped out per beat, and the number of heart beats per minute (heart rate (HR)) (Vincent, 2008). The arterial-venous oxygen difference (a-vO2 diff) is the difference between the oxygen concentration of the arterial and mixed venous blood (Manley, 1996). An individual's aerobic capacity or maximum oxygen uptake (VO2max) is a function of, and thus limited by, the ability of the cardiovascular system to supply (QT) and/or the skeletal muscles to use (a-vO2 diff) oxygen (Manley, 1996, Jakovljevic et al., 2012a). Thus after a period of training, an observed improvement in VO2peak is contributed to by improvement in QT and a-vO2diff to varying degrees. Dependent on training modality, skeletal muscles undergo fiber hypertrophy and hyperplasia and increased recruitment (Manley, 1996). Endurance training also facilitates a greater capacity for blood flow in skeletal muscles by increasing the numbers of capillaries (Prior et al., 2004). Thus it could be postulated that in our population the improvements seen in VO2peak, without significant associated cardiac

changes could be due to a greater contribution of improvement in a-vO2diff rather than QT. This could be due to the type of exercise training used or the physiological response in individuals with PD.

6.1.3 Discussion: Effect of an exercise intervention on pulmonary function and respiratory muscle strength

Very little research had been done previously looking at the effect of exercise on pulmonary function in PD. A small study by Koseoglu et al, looked at the effect of pulmonary rehabilitation in PD on pulmonary function test results and whilst trends of improvement existed, the results failed to reach statistical significance which may have been due to the small number of participants and the intervention length of 5 weeks only (Koseoglu et al., 1997). A further small study measured respiratory muscle strength and endurance, perception of dyspnoea and quality of life in 20 PD patients, Hoehn and Yahr stages II-III. The patients were then divided into 2 groups of 10, 1 group received 12 weeks of ½ hour, 6 times per week specific inspiratory muscle training and the other group received sham training. Significant improvements in inspiratory muscle strength, endurance and perception of dyspnoea were seen only in the intervention group (Inzelberg et al., 2005).

As highlighted in table 21, in both the control and intervention groups, the inspiratory muscle strength tests (MIP and SNIP) were worse than the expiratory muscle strength test (MEP) and in addition to this, SNIP was again worse than MIP. In both the control and the intervention groups, no statistically significant changes were seen in percent predicted values of FEV1, FVC, PEF, MEP, MIP and SNIP. Whilst there was a trend in the intervention group of an improvement post exercise intervention in percent predicted MIP, this unfortunately did not reach statistical significance and was also not reflected in the SNIP results.

While exercise produces short term responses to meet immediate demand, exercise training produces long term adaptations. These adaptations include cardiovascular, respiratory, skeletal muscles, bone, metabolic and hormonal adaptations. The magnitude of these adaptations depends on a number of factors including pre-exercise fitness level, type of exercise programme, intensity and duration. Respiratory adaptations with training are predominantly an increase in pulmonary ventilation and an increase in pulmonary diffusion

during maximal exertion. With this in mind, this study may have failed to reach statistical significance in changes in lung function and respiratory muscle strength for a number of reasons. The effort dependent indices selected to review as outcome measures may not best reflect pulmonary ventilation and would not reflect pulmonary diffusion where the most benefit is likely to occur. The modest numbers in the RCT section of study may have impacted on the results. The type of exercise intervention and programme designed was not specifically targeting respiratory muscles and thus significant improvements in MEP, MIP and SNIP were not seen. Noting the trend in the increase in MIP in this study in the intervention group, and the significant improvements in inspiratory muscle strength, endurance and perception of dyspnoea in response to inspiratory muscle training observed by Inzelberg et al, raises the question about the potential role of inspiratory muscle training in this group. Further to this, potential exists for a role for expiratory muscle training, upper extremity exercise and pulmonary rehabilitation style training to assess if these improve pulmonary function and respiratory muscle strength in PD.

6.1.4 Discussion: Effect of an exercise intervention on parkinsonian symptoms, Parkinson's disease stage, quality of life, sleep, anxiety and depression

While Parkinson's disease stage, as defined by Hoehn and Yahr, remained the same after the 12 week exercise intervention, statistically significant changes from baseline after the 12 weeks of exercise or normal care were only seen in the intervention group as improvements in UPDRS 1 and 2 section scores. The intervention group change from baseline UPDRS part 1 score improved by -1.0 point and the UPDRS part 2 score improved by -2.0 points. Although not reaching statistical significance, the UPDRS section 3 in the intervention group changed from baseline by a median improvement of -2.0 points. Following the exercise intervention in the intervention group or 12 weeks normal care in the control group, statistically significant results were only seen in the intervention group and these were as improvements in the PDQ 39 single index, SCOPA C, SCOPA D, HADS A and HADS D scores. The median change from baseline in the intervention group for these parameters was -2.2 for the PDQ 39 single index, -1.0 for overall quality of night time sleep, -1.0 for sleepiness in the daytime and evenings, -1.0 for anxiety and -1.0 for depression. Thus structured

exercise therapy in PD improves parkinsonian symptoms, quality of life, sleep, anxiety and depression and is an important therapy to improve wellbeing and health.

The mechanism for how exercise in healthy individuals and in those with diseases, including PD, improves these symptoms is complex and still not fully understood with a number of potential philosophies. Neurotrophins most likely play a significant role and research interest in them has increased over recent years. To date no pharmacological treatments have been shown to be unequivocally neuroprotective in PD (Ahlskog, 2011). Exercise is known to provoke a surge of molecular and cellular processes that support brain plasticity. Activity dependent neuroplasticity is supported by neurotrophins, which have the ability to signal neurons to survive, differentiate and grow (Hennigan et al., 2007, Johnston, 2009, Neeper et al., 1995, Neeper et al., 1996, Vaynman and Gomez-Pinilla, 2005). Brain derived neurotrophic factor (BDNF) seems to be the most susceptible neurotrophin to regulation by exercise (Johnston, 2009, Neeper et al., 1995, Vaynman and Gomez-Pinilla, 2005) Studies have shown decreased BDNF expression within the substantia nigra of PD brains as compared to controls (Howells et al., 2000, Parain et al., 1999). A common single nucleotide polymorphism (SNP) in the BDNF gene, G196A, results in a methionine- valine substitution at codon 66 (Val66Met). The presence of this minor allele leads to reduced depolarisation induced secretion of BDNF from neuronal cells (Egan et al., 2003, Chen et al., 2004). With this neural plasticity in mind Fox et al, succinctly summarised philosophies of how exercise enhances neuroplasticity in PD; intense activities maximise synaptic plasticity, complex activities encourage greater structural adaptation, rewarding activities increase dopamine levels, dopaminergic neurons are highly responsive to exercise and notably that exercise in addition to improving symptoms when the disease is already present can also retard the onset of PD (Fox et al., 2006, Archer et al., 2011).

It must also be remembered that the effects may be “knock on” effects, for example poor sleep and early morning waking can be associated depression, thus improving depression may also improve sleep. Similarly if parkinsonian symptoms are disturbing individual’s sleep, if exercise improves the parkinsonian symptoms the sleep may also improve. Previous studies, as highlighted in a meta-analysis, indicate that regular exercise increases total

sleep time and self-reports epidemiological data support that acute and chronic exercise promotes sleep (Kubitz et al., 1996, Driver and Taylor, 2000). The exact mechanisms of how exercise improves sleep are not fully understood and most studies reporting the effects of exercise on sleep have predominantly included young sleepers without problematic sleep. As described and discussed the pathophysiology of how exercise improves outcomes such as sleep, anxiety and depression is not fully understood and remains complex with a significant amount of overlap.

6.1.5 Discussion: Heart rate response to exercise

The RCT was primarily designed to look at the long term adaptations to exercise training, however had the benefit of also being able to assess the short term response to exercise to meet immediate demand during a maximal cardiopulmonary exercise test. In both the control and intervention groups, pre and post the intervention or normal care 12 weeks, the peak heart rate achieved during the maximal cardiopulmonary exercise tests was significantly lower than the predicted value. At baseline and follow up, each group median peak heart rate was below 77% predicted. This result was not reflected in the median VO2peaks achieved, at baseline and follow up, in each group which were equal to or exceeded 90% predicted. This result was not significantly affected when individuals on rate limiting medication were excluded.

As discussed in section 2.4, An individual's aerobic capacity or maximum oxygen uptake (VO2max) is a function of, and thus limited by, the ability of the cardiovascular system to supply (QT) and/or the skeletal muscles to use (a-vO2 diff) oxygen (Manley, 1996, Jakovljevic et al., 2012a). As work increases the QT increases in an almost linear pattern up to a maximum, this occurs due to increases in heart rate (HR) and stroke volume (SV) (Manley, 1996). Although both HR and SV increase with exertion, the contribution to the increase QT is much greater from the increase in HR particularly at high exertion (Higginbotham et al., 1986). Maximal achievable heart rate (HRmax) is considered to be related to age and although there a numerous prediction equations, HRmax = 220-age is commonly accepted and used (Robergs and Landwher, 2002).

Given that all participants achieved anaerobic threshold and the median VO2 peaks achieved exceeded 90% predicted, it is very unlikely that the poor heart

rate response to exercise seen was related to effort or the choice of CPET modality with the bicycle causing leg fatigue and early termination of an exercise test. As such it must be considered that there are other potential causes for a poor heart rate response to exercise in PD patients. It is likely that chronotropic incompetence, the inability of the heart to increase its rate with increased activity or demand is the cause. Chronotropic incompetence, common in cardiovascular disease, causes exercise intolerance, deterioration in quality-of-life and very importantly is an independent predictor of adverse cardiovascular events and overall mortality (Brubaker and Kitzman, 2011). With the dysautonomia in PD known to involve the cardiovascular system, involving postganglionic sympathetic noradrenergic lesions, norepinephrine loss in the sympathetic nervous system of the heart and parasympathetic over activity it seems very plausible that this is the cause of chronotropic incompetence in PD and the resultant poor heart rate response to exercise.

These findings need to be explored further to examine the stability of heart rate during exercise and the recovery response of the heart rate to stopping exercise in PD. This is a notably interesting finding as it raises questions about the heart rate response of those with PD in other situations and as clinicians our assessment of them. Given these findings it would be important to consider implications such as heart rate in response to sepsis, and if blunted we may be underestimating the severity of illness in this population with resultant effects on morbidity and mortality. This is an area which warrants significant further research.

6.2 Strengths and limitations

There were limitations to the study; although exceeding or comparable number to previous studies, increasing the number of participants in future studies would improve power. It would have been beneficial to assess heart rate response during the exercise intervention, this was attempted however the equipment used proved complex for the participants to use and unreliable, thus produced no interpretable data. As described in section 4.5 the capillary blood gas sampling was unsuccessful. The patient information sheet detailed the use of a swallow assessment device and a device that measures oxygen levels (sats) during sleep, unfortunately the swallow assessment devices were not available on commencement of the study and the sats devices did not provide

meaningful results. The sats devices were patient operated and could not be pre-programmed, unfortunately the participants struggled with setting the devices to monitor oxygen levels only overnight resulting in devices recording no data or continuous data for days making the results uninterpretable. Given the broad ranging nature of the variables studied it was decided not to apply corrections for multiple comparisons. On balance it was felt that each variable considered was sufficiently unique and so no two variables were from the same family, to make correction for multiple comparisons unnecessary. A blanket adjustment would be too conservative an approach and likely wrongly show lack of significance. This is however acknowledged as a limitation as it is important to recognise that in some cases significance may have been over estimated for this reason.

In research when discussing results we refer to statistically significant changes, however this is different to clinically significant changes in outcome scores and this has to be taken into account as in some cases statistically significant change has little clinical significance. Minimal clinically important differences (MCID) are patient derived scores, that generally involve patient perception, that reflect changes that are meaningful for the patient. There is considerable confusion in the literature with terminology used interchangeably which is actually quite different for example MCID, the minimally important difference (MID), the minimal clinical difference (MCD) or the minimal clinically significant difference (MCSD). There is little consensus about defining MCID across the majority of outcome tools for a variety of reasons. There are a number of different methods to formulate a MCID due to different influencing factors. Baseline severity of symptoms can influence MCID of an outcome tool as can the use of the same tool in different study populations (Cook, 2008). As highlighted in section 5.10 when discussing 6MWT, with the same applying to VO2peak, SCOPA SLEEP and HADS, when outcome measures are used in different populations the MCID will vary for example the MCID for HADS following an exercise intervention in chronic heart failure will be different to that following an exercise intervention in PD. While the UPDRS and PDQ-39 are specific for use in PD, MCID estimates have not been fully established with papers quoting different estimates. More recent studies suggest for the UPDRS part 3 MCID for improvement was -3.25 and worsening 4.63, the UPDRS part 1 MCID for improvement was -2.64 and worsening 2.45 and the UPDRS part 2

MCID for improvement was -3.05 and worsening 2.51 (Horvath et al., 2015, Shulman et al., 2010). A recent large study quoted estimates for MCID thresholds for PDQ-39-SI were -4.72 and +4.22 for minimal clinically important improvement and worsening respectively however acknowledged MICD estimates varied across PD severity. This all has to be taken into account when interpreting results (Horvath et al., 2017).

The RCT benefitted from a number of strengths including gold standard pulmonary function and cardiorespiratory fitness testing, the exercise intervention was supervised and the study provided the means to assess short term and long term responses to exercise. Perhaps most importantly the exercise intervention received markedly positive feedback from the participants, with a number continuing voluntarily at the same healthy living centre for a further 12 weeks and then subsequently joining fitness centres. I feel one quote from a patient from the intervention group sums up the most important strength of the study “taking part in this has changed my life”.

6.3 Conclusion

Reflecting back to the hypothesis, aims and objectives, the RCT has shown that a structured exercise intervention in PD improves cardiorespiratory fitness, exercise capacity, parkinsonian symptoms, quality of life, sleep, anxiety and depression. Further research needs to be done to establish the optimum “exercise prescription” to maximise these benefits and also provide benefits in pulmonary function and respiratory muscle strength.

Secondly the fascinating observation on poor heart rate response to exercise warrants significant further research.

Chapter 7. Conclusion and future studies

7.1 Overall conclusions

The cross-sectional study and the RCT both provided fascinating results and provoked questions for further research. Both sections of the study fulfilled the aims and objectives set out. The results of the cross-sectional study have shown a notable prevalence of obstructive spirometry, upper airways obstruction and inspiratory muscle weakness in this population. This pattern was observed in both non-smokers and smokers or those with known obstructive lung disease. This pattern of dysfunction of the respiratory system could lead to increased morbidity and mortality. The RCT has shown that a structured exercise intervention in PD improves cardiorespiratory fitness, exercise capacity, parkinsonian symptoms, quality of life, sleep, anxiety and depression. This study provides evidence in support of structured exercise as a treatment for PD. A secondary interesting finding in the RCT was the observation of poor heart rate response to exercise, this raises questions about heart rate response in PD to other stimuli such as sepsis. These significant findings warrant further research.

7.2 Future studies

The results from both the cross-sectional study and the RCT have proved very thought provoking with ideas for future studies. Further research is indicated to look at any association between pulmonary dysfunction in IPD and a number of issues including; bulbar problems, speech, swallowing, drooling, night time sleep, daytime somnolence and sleep disorders. Rehabilitation of pulmonary dysfunction warrants further assessment by pulmonary rehabilitation, specific respiratory muscle training and alternative exercise interventions. In addition to these non-pharmacological therapies, the effect of dopaminergic therapy on pulmonary function should be further studied.

Considering exercise therapy, further research needs to be done to establish the optimum “exercise prescription” to maximise benefits and also provide benefits in pulmonary function and respiratory muscle strength. Interventions such as high-intensity interval training could be considered for research in this population as the short bursts of exertion may suit this population who may fatigue easily. Finally, the observation on poor heart rate response to exercise warrants significant further research.

Appendix A. Cross-sectional study; participant information sheet, consent form and assessment document

Professor Richard Walker
North Tyneside General Hospital
Rake Lane
North Shields
NE29 8NH
Tel: 0191 293 2709

PARTICIPANT INFORMATION SHEET

EXERCISE AND PULMONARY FUNCTION IN IDIOPATHIC PARKINSON'S DISEASE
BASELINE PULMONARY FUNCTION GROUP

We would like to invite you to take part in this research study. Please take time to read the following information carefully, it explains why the research is being done and what it involves. If you have any questions about the information or if there is anything you do not understand, you are very welcome to ask for further explanation.

- Part 1 tells you the purpose of the study and what will happen if you decide to take part.
- Part 2 gives you more detailed information about the conduct of the study.

Thank you for reading this.

PART 1

What is the purpose of the research study?

Parkinson's disease (PD) is the second most common neurodegenerative condition in the UK. Many people with PD suffer from respiratory symptoms including shortness of breath on exertion, cough and sputum production. Respiratory complications with PD are a common reason for hospital admission. Previous research studies looking at lung function in PD have produced some conflicting results.

We plan to undertake a large study to look at the lung function and breathing muscle strength in PD. By defining the pattern of any lung problems we hope our results can be used to improve management, potentially non pharmacologically and pharmacologically, and reduce breathing complications and hospital admissions.

Why have I been invited to participate?

You have been invited to participate as you are a patient with Idiopathic Parkinson's Disease (IPD) currently under the care of the Northumbria PD service, the team organising this study.

Do I have to take part?

No, your participation is purely voluntary. If you do decide to take part, you are still free to withdraw at any time without giving reasons. A decision not to take part or to withdraw will not affect the standard of care you receive. If you do decide to take part, you will be given this information sheet to keep and then be asked to sign a consent form.

What will the research study involve?

You will be asked to attend North Tyneside General Hospital (NTGH) twice and we aim to recruit 100 participants.

VISIT 1 – NTGH, JUBILEE DAY HOSPITAL
This visit will involve taking a medical history and brief examination, questionnaires about your Parkinson's Disease, exercise and breathing. You will have an ECG (heart tracing). You will have a blood test. **Total visit time: 120 minutes**

VISIT 2 – NTGH, PULMONARY FUNCTION
This visit will involve measurements of how your lungs work, their volume and the strength of the breathing muscles. These are painless assessments involving breathing in and out of a tube attached to machines that record the measurements. **Total visit time: 35 minutes**

BLOOD TEST
At visit 1 you will have a blood test. This blood test is a simple pin prick test called a Capillary Blood gas that measures the levels of oxygen and carbon dioxide in the blood.

After full completion of the study, all participants will be invited to a formal feedback event to share the overall results of the study.

Expenses and payments

Travel costs will be reimbursed by mileage, public transport or taxi as appropriate.

What are the possible risks/ disadvantages of taking part?

Giving up time to participate has to be considered.

What are the possible benefits of taking part?

You will be contributing valuable information about how the lungs work in PD. Appropriate action will be taken for abnormal results if necessary.

Contact details:

Dr Ailish O'Callaghan or Professor Richard Walker, Department of Medicine, North Tyneside General Hospital, Rake Lane, North Shields. NE29 8NH. Tel: 0191 293 2709

This completes Part 1 of the information sheet. Thank you for reading Part 1 and if you are interested in participating in the study please continue to Part 2 before making a decision.

PART 2

What will happen if I don't want to carry on with the study?

You can withdraw from the study at any time. The data already collected could still be used if you were agreeable to this.

What if there is a problem?

a) Concerns or complaints – If you have a concern or complaint about any aspect of this study you should contact Dr O'Callaghan or Professor Walker by phone on 0191 293 2709 or in writing at the address above. The NHS operated Patient Advice and Liaison Service (PALS) can also provide guidance with any complaints or concerns by phone on 0800 032 0202, Text/SMS: 01670511098 or by email northoftynepals@nhct.nhs.uk

b) In the unlikely event that something does go wrong and you suffer in any way the arrangements are as follows. If negligence of staff led to harm, this would be covered by the Northumbria Healthcare NHS Foundation Trust clinical negligence scheme. You may have to meet legal costs.

Will my taking part in the study be kept confidential?

All information obtained during the course of the study will be kept strictly confidential. It is our duty by law to protect your personal information and all of our procedures for handling, processing, storing and destroying data are compliant with the Data Protection Act (1998). Data collected during the study and your medical records may be looked at by regulatory authorities, who check that research is being carried out correctly, and the NHS Trust where it is relevant to your participation in the research.

Results will be presented at scientific meetings, published in scientific journals and presented to participants at a feedback event without any personal identification.

Will my General Practitioner (GP) be involved?

Your GP will be informed of your help with this study. This is standard practice.

What will happen to blood samples?

The blood sample will be tested for Capillary Blood Gas analysis (measures the gases in the blood). Samples will be disposed of once analysed.

What will happen to the results of the research?

The results will be published in scientific journals and presented at scientific meetings. All participants will be invited to a formal feedback event at which the results will be presented.

Who is organising and funding the research?

The study is being undertaken as part of Dr Ailish O'Callaghan's MD degree at Newcastle University. The funding is from Northumbria Healthcare NHS Foundation Trust and via grants from Parkinson's UK and The British Geriatrics Society.

Who has reviewed the study?

Ethical review of this study has been conducted by the Newcastle North Tyneside 1 Research Ethics Committee.

Further information and contact details

You can get further information on this study by contacting Dr Ailish O'Callaghan or Professor Richard Walker, Department of Medicine, North Tyneside General Hospital, Rake Lane, North Shields, NE29 8NH. Tel: 0191 293 2709.

For further independent information about being involved in a research study please contact the Patient Advice and Liaison Service (PALS). Freephone 0800 0320202, email: northoftynepals@nhct.nhs.uk Text/SMS: 01670511098

THANK YOU VERY MUCH FOR YOUR TIME AND INTEREST

Patient Identification number for this trial:

CONSENT FORM

Title of project: **Exercise and pulmonary function in Idiopathic Parkinson's disease**

Baseline pulmonary function group

Name of researcher: **Professor Richard Walker, North Tyneside General Hospital,**
Tel: **0191 293 2709**

Please initial box

1. I confirm that I have read and understand the information sheet dated 21st May 2012(V1.2) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. If I choose to withdraw from the study or do not continue in the study for other reasons, I consent to the use of the data already collected. ☐

4. I agree to my GP being informed of my participation in the study. ☐

5. I understand that data collected during this study and my medical records may be looked at by individuals from regulatory authorities or from the NHS Trust where it is relevant to my participation in this research. I give permission for those individuals to access my data. ☐

6. I agree to being contacted on the following telephone number: ☐
……

7. I agree to take part in the above study. ☐

……	……	……
Name of participant	Date	Signature
……	……	……
Name of person taking consent (if different from researcher)	Date	Signature
……	……	……
Researcher	Date	Signature

ID NUMBER…… VISIT NUMBER…….. DATE……..

EXERCISE AND PULMONARY FUNCTION IN IPD ASSESSMENT

AGE ……YRS HEIGHT……M WEIGHT……KG

PARKINSON'S DISEASE

1. DISEASE DURATION……..YRS

SYMPTOMS AT ONSET	RIGHT	LEFT
BRADYKINESIA		
RIGIDITY		
TREMOR		
POSTURAL INSTABILITY		

2. CURRENT PD MEDS……..SCHEDULE……DATE STARTED

3. PREVIOUS PD MEDS……DATE STOPPED

4. HALLUCINATIONS IN LAST WEEK? YES NO
   IF YES FREQUENCY?
   TYPE? VISUAL/ AUDITORY/ OLFACTORY/ GUSTATORY/ TACTILE

5. SYMPTOMS SUGGESTIVE OF RBD? YES NO

6. HISTORY SENSE OF SMELL LOSS? YES NO

7. HISTORY OF COMPULSIVE BEHAVIOR? YES NO

8. SCANS? YES NO
   MRI/ CT/ DAT (FPCIT SPECT)
   RESULT?

PAST MEDICAL HISTORY/ PAST SURGICAL HISTORY

9. HISTORY OF CARDIOVASCULAR DISEASE? YES NO
   MI/IHD/ANGINA/CABG/ANGIO
   DETAILS……..

10. HISTORY OF STROKE/TIA/PVD YES NO
    DETAILS……

11. HISTORY OF HYPERTENSION OR DYSLIPIDAEMIA? YES NO
    DETAILS……..

12. HISTORY OF DIABETES? YES NO
    DETAILS……

13. HISTORY OF PULMONARY DISEASE? YES NO
    DETAILS……

14. HISTORY OF JOINT PROBLEMS? YES NO
    DETAILS……

15. KNOWN THORACIC/ABDO/AORTIC ANEURYSM? YES NO
    DETAILS……

16. HISTORY PNEUMOTHORAX/ HAEMOPTYSIS? YES NO
    DETAILS……

17. RECENT SURGERY (ALL/EYE/THORACIC/ABDO)? YES NO
    DETAILS……

18. HISTORY BLOOD CLOT/DVT/PE? YES NO
    DETAILS……

19. PREGNANT? YES NO

MEDICATION OTHER THAN FOR PARKINSON'S DISEASE

ALLERGIES YES NO

DETAILS……

FAMILY HISTORY

PARKINSONISM/ PD/ PD PLUS/ TREMOR/ NEURO/ CARDIAC/
STROKE/
PULMONARY/ MALIGNANCY
DETAILS……

SOCIAL HISTORY

SMOKER YES NO
EX
PACK
YEARS……
COMMENTS (E.G. PIPE ETC)……

OCCUPATIONS.……
PETS……

ALCOHOL
(UNITS/WEEK)……..

EXERCISE HISTORY

INEXCLUDING WALKING:
FREQUENCY/ WEEK 0 1 2 3 4 5 6 7 8 9 10
DURATION (MINS) 10 20 30 40 50 60 70 80 90
TYPES OF EXERCISE
DETAILS……..

ON EXAMINATION

HEART SOUNDS/JVP PULSE……..

LUNGS/ LEGS BP……

ABDOMEN SATS……..

Appendix B. Rating scales

Due to copyright and reproduction prohibitions, copies of rating scales cannot be reproduced.

The MDS-UPDRS can be accessed via this URL:
http://www.movementdisorders.org/MDS-Files1/PDFs/Rating-Scales/MDS-UPDRS_Vol23_Issue15_2008.pdf

The PDQ-39 can be accessed via this URL:
https://innovation.ox.ac.uk/wp-content/uploads/2014/07/Final_PDQ-39_English_UK_SAMPLE.pdf

The SCOPA-SLEEP can be accessed via this URL:
https://www.lumc.nl/sub/7020/att/1288981/SCOPA-SLEEP-EN

The HADS can be accessed via this URL:
http://www.scalesandmeasures.net/files/files/HADS.pdf

Appendix C. Randomised control trial; participant information sheet, consent form and assessment document

Professor Richard Walker
North Tyneside General Hospital
Rake Lane
North Shields
NE29 8NH
Tel: 0191 293 2709

PARTICIPANT INFORMATION SHEET

EXERCISE AND PULMONARY FUNCTION IN IDIOPATHIC PARKINSON'S DISEASE RANDOMISED CONTROL TRIAL GROUP

We would like to invite you to take part in this research study. Please take time to read the following information carefully, it explains why the research is being done and what it involves. If you have any questions about the information or if there is anything you do not understand, you are very welcome to ask for further explanation.

- Part 1 tells you the purpose of the study and what will happen if you decide to take part.
- Part 2 gives you more detailed information about the conduct of the study.

Thank you for reading this.

PART 1

What is the purpose of the research study?

Parkinson's disease (PD) is the second most common neurodegenerative condition in the UK. Many people with PD suffer from respiratory symptoms including shortness of breath on exertion, cough and sputum production. Respiratory complications with PD are a common reason for hospital admission. Previous research studies looking at lung function in PD have produced some conflicting results.

We plan to undertake a large study to look at the lung function and breathing muscle strength in PD and to assess the effect of a 12 week exercise programme on the above measurements. By defining the pattern of any lung problems in PD and demonstrating the effect of exercise on the heart and lung's function and on quality of life measures, we hope our results can be used to improve management and reduce breathing complications and hospital admissions.

Why have I been invited to participate?

You have been invited to participate as you are a patient with Idiopathic Parkinson's Disease (IPD) currently under the care of the Northumbria PD service, the team organising this study.

Do I have to take part?

No, your participation is purely voluntary. If you do decide to take part, you are still free to withdraw at any time without giving reasons. A decision not to take part or to withdraw will not affect the standard of care you receive. If you do decide to take part, you will be given this information sheet to keep and then be asked to sign a consent form.

What will the research study involve?

You will be asked to attend North Tyneside General Hospital (NTGH) twice and the Clinical Research Facility at the Royal Victoria Infirmary (RVI) once at the beginning of the study and then NTGH twice and the RVI once again after 12 weeks. If you are allocated to the exercise group, during that 12 week period you will also be asked to attend 45 minute supervised exercise sessions 3 times per week at Moor Park Healthy Living Centre (HLC), approximately 1.5 miles from NTGH.

We aim to recruit 30 participants and you will be divided at random into 2 equal groups, 1 group that will receive the 12 week exercise programme and 1 group that will continue to receive normal care. If you are placed in the group which does not attend the exercise sessions, at the end of the study you will be offered the opportunity to participate in a 12 week exercise programme if you would like to.

VISIT 1 – NTGH, JUBILEE DAY HOSPITAL
This visit will involve taking a medical history and examination, questionnaires about your Parkinson's disease, exercise, breathing, quality of life, sleep, memory, anxiety and depression. You will have a speech assessment, involving measuring the maximum volume of your voice and recording you reading 5 sentences and a swallow assessment involving drinking a glass of water. You will have a 6 minute walking assessment. You will have an ECG (heart tracing). The normal care group will have 2 blood tests and the exercise group will have 1 blood test. The exercise group will go home wearing an accelerometry sensor (wristwatch type device) that measures movement and a small earpiece device that measures swallow. These devices can be dropped back at NTGH or collected by a member of the research team the following day. **Total visit time: 210 minutes**

VISIT 2 – NTGH, PULMONARY FUNCTION
This visit will involve measurement of how your lungs work, their volume and the strength of the breathing muscles. These are painless assessments involving breathing in and out of a tube attached to machines that record the measurements. **Total visit time: 35 minutes**

VISIT 3 – RVI
This visit will involve checks of your pulse, blood pressure and strength, a memory test and a cycling test. The cycling test will be done on a recliner bike. During this test you will cycle at the same pace but how hard you are cycling will steadily increase. You will keep on cycling until you decide to stop or pedalling becomes too difficult. Whilst you are cycling you will be asked to wear a breathing mask and heart monitor. The exercise test will last 10 – 15 minutes. **Total visit time: 75 minutes**

12 WEEK EXERCISE INTERVENTION – HLC
If you are allocated to the exercise group we will ask you to attend the Moor Park HLC for 45 minute sessions 3 times per week for 12 weeks. You will be in groups of 5 and the HLCs will be closed to the general public during your sessions. The sessions are individually tailored and supervised by the HLC staff who have extensive experience and qualifications in exercise in those with medical problems. Each 45 minute session will comprise 30 minutes of aerobic exercise, for example including cycling, and 15 minutes of resistance exercise, for example including arm weights. Before and after your first and last sessions you will have a blood test. During the first and last weeks you will go home from one of the sessions with a wristwatch type device that measures your oxygen level while you sleep. **Each visit time: 45 minutes**

VISIT 4 – NTGH
The same as visit 1. **Total visit time: 210 minutes**

VISIT 5 – NTGH
The same as visit 2. **Total visit time: 35 minutes**

VISIT 6 – RVI
The same as visit 3. **Total visit time: 75 minutes**

BLOOD TESTS

At visits 1 and 4 the normal care group will have 2 blood tests; 1 a simple pin prick test to measure the levels of the different gases in the blood and 1 to measure the blood count and the level and genotype (the genetic makeup) of a protein released in response to exercise into the blood. At visit 1 and 4 the exercise group will have 1 blood test, a simple pin prick test to measure the levels of the gases in the blood.

In the exercise group only, before and after your first and last exercise sessions you will have a simple blood test for the blood count and the level and genotype (genetic makeup) of a protein in the blood that is affected by exercise.

After full completion of the study, all participants will be invited to a formal feedback event to share the overall results of the study.

Expenses and payments

Travel costs will be reimbursed by mileage, public transport or taxi as appropriate.

What are the possible risks/ disadvantages of taking part?

Giving up time to participate has to be considered.

What are the possible benefits of taking part?

It is hoped that participants may feel the benefits of becoming physically fitter during the study. You will have supervised exercise sessions, like a personal trainer, which will teach you about your body and show you how to exercise and use the equipment correctly.

Contact details:

Dr Ailish O'Callaghan or Professor Richard Walker, Department of Medicine, North Tyneside General Hospital, Rake Lane, North Shields. NE29 8NH
Tel: 0191 293 2709

This completes Part 1 of the information sheet. Thank you for reading Part 1 and if you are interested in participating in the study please continue to read Part 2 before making any decision.

PART 2

What will happen if I don't want to carry on with the study?

You can withdraw from the study at any time. The data already collected could still be used if you were agreeable to this.

What if there is a problem?

a) Concerns or complaints – If you have a concern or complaint about any aspect of this study you should contact Dr O'Callaghan or Professor Walker by phone on 0191 293 2709 or in writing at the address above. The NHS operated Patient Advice and Liaison Service (PALS) can also provide guidance with any complaints or concerns by phone on 0800 032 0202, Text/SMS: 01670511098 or by email northoftynepals@nhct.nhs.uk

b) In the unlikely event that something does go wrong and you suffer in any way the arrangements are as follows. If negligence of staff led to harm, then dependent on hospital site this would be covered by either the Northumbria Healthcare NHS Foundation Trust clinical negligence scheme or the Newcastle upon Tyne Hospitals NHS Foundation Trust clinical negligence scheme. You may have to meet legal costs.

Will my taking part in the study be kept confidential?

All information obtained during the course of the study will be kept strictly confidential. It is our duty by law to protect your personal information and all of our procedures for handling, processing, storing and destroying data are compliant with the Data Protection Act (1998). Data collected during the study and your medical

records may be looked at by regulatory authorities, who check that research is being carried out correctly, and the NHS Trust where it is relevant to your participation in the research.

As part of your speech assessment you will be recorded reading 5 sentences. We will give each recording a code to make it as anonymous as possible. These recordings will be analysed by a speech and language therapist and destroyed after analysis.

Results will be presented at scientific meetings, published in scientific journals and presented to participants at a feedback event without any personal identification.

Will my General Practitioner (GP) be involved?

Your GP will be informed of your help with this study. This is standard practice.

What will happen to blood samples?

The blood samples will be tested for Full Blood Count (counts the cells in the blood), Brain Derived Neurotrophic Factor (a protein released in response to exercise that may improve the ability of the brain's neurons to survive and grow) level and genotype and Capillary Blood Gas analysis (measures the gases in the blood). Samples for Full Blood Count and Brain Derived Neurotrophic Factor will be stored until it is certain that the test results are accurate and then they will be disposed of. Samples for Capillary Blood Gas are disposed of after analysis.

What will happen to the results of the research?

The results will be published in scientific journals and presented at scientific meetings. All participants will be invited to a formal feedback event at which the results will be presented.

Who is organising and funding the research?

The study is being undertaken as part of Dr Ailish O'Callaghan's MD degree at Newcastle University. The funding is via Northumbria Healthcare NHS Foundation Trust and grants from Parkinson's UK and The British Geriatrics Society.

Who has reviewed the study?

Ethical review of this study has been conducted by the Newcastle North Tyneside 1 Research Ethics Committee.

Further information and contact details

You can get further information on this study by contacting Dr Ailish O'Callaghan or Professor Richard Walker, Department of Medicine, North Tyneside General Hospital, Rake Lane, North Shields, NE29 8NH. Tel: 0191 293 2709.

For further independent information about being involved in a research study please contact the Patient Advice and Liaison Service (PALS). Freephone 0800 0320202, email: northoftynepals@nhct.nhs.uk Text/SMS: 01670511098

THANK YOU VERY MUCH FOR YOUR TIME AND INTEREST

Northumbria Healthcare NHS
NHS Foundation Trust

Newcastle University

Patient Identification number for this trial:

CONSENT FORM

Title of project: **Exercise and pulmonary function in Idiopathic Parkinson's disease**

Randomised control trial group

Name of researcher: **Professor Richard Walker, North Tyneside General Hospital,**
Tel: **0191 293 2709**

Please initial box

1. I confirm that I have read and understand the information sheet dated 21st May 2012(V1.2) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. If I choose to withdraw from the study or do not continue in the study for other reasons, I consent to the use of the data already collected. ☐

4. I agree to my GP being informed of my participation in the study. ☐

5. I understand that data collected during this study and my medical records may be looked at by individuals from regulatory authorities or from the NHS Trust where it is relevant to my participation in this research. I give permission for those individuals to access my data. ☐

6. I agree to being contacted on the following telephone number: ☐
……

7. I agree to take part in the above study. ☐

……..	……	……
Name of participant	Date	Signature
……..	……	……
Name of person taking consent (if different from researcher)	Date	Signature
……..	……	……
Researcher	Date	Signature

ID NUMBER…… VISIT NUMBER……. DATE…….

EXERCISE AND PULMONARY FUNCTION IN IPD ASSESSMENT

AGE ……YRS HEIGHT……M WEIGHT……KG

PARKINSON'S DISEASE

1. DISEASE DURATION……..YRS

SYMPTOMS AT ONSET	RIGHT	LEFT
BRADYKINESIA		
RIGIDITY		
TREMOR		
POSTURAL INSTABILITY		

2. CURRENT PD MEDS……SCHEDULE……...DATE STARTED

3. PREVIOUS PD MEDS……DATE STOPPED

4. HALLUCINATIONS IN LAST WEEK? YES NO
   IF YES FREQUENCY?
   TYPE? VISUAL/ AUDITORY/ OLFACTORY/ GUSTATORY/ TACTILE

5. SYMPTOMS SUGGESTIVE OF RBD? YES NO

6. HISTORY SENSE OF SMELL LOSS? YES NO

7. HISTORY OF COMPULSIVE BEHAVIOR? YES NO

8. SCANS? YES NO
   MRI/ CT/ DAT (FPCIT SPECT)
   RESULT?

PAST MEDICAL HISTORY/ PAST SURGICAL HISTORY

9. HISTORY OF CARDIOVASCULAR DISEASE? YES NO
   MI/IHD/ANGINA/CABG/ANGIO
   DETAILS……

10. HISTORY OF STROKE/TIA/PVD YES NO
    DETAILS……

11. HISTORY OF HYPERTENSION OR DYSLIPIDAEMIA? YES NO
    DETAILS……

12. HISTORY OF DIABETES? YES NO
    DETAILS……

13. HISTORY OF PULMONARY DISEASE? YES NO
    DETAILS……

14. HISTORY OF JOINT PROBLEMS? YES NO
    DETAILS……

15. KNOWN THORACIC/ABDO/AORTIC ANEURYSM? YES NO
    DETAILS……

16. HISTORY PNEUMOTHORAX/ HAEMOPTYSIS? YES NO
    DETAILS……

17. RECENT SURGERY (ALL/EYE/THORACIC/ABDO)? YES NO
    DETAILS……

18. HISTORY BLOOD CLOT/DVT/PE? YES NO
    DETAILS……

19. PREGNANT? YES NO

MEDICATION OTHER THAN FOR PARKINSON'S DISEASE

ALLERGIES YES NO

DETAILS……

FAMILY HISTORY

PARKINSONISM/ PD/ PD PLUS/ TREMOR/ NEURO/ CARDIAC/ STROKE/
PULMONARY/ MALIGNANCY
DETAILS……

SOCIAL HISTORY

SMOKER YES NO
EX
PACK
YEARS……
COMMENTS (E.G. PIPE ETC)……
OCCUPATIONS……..
PETS……
ALCOHOL
(UNITS/WEEK)……..

EXERCISE HISTORY

INEXCLUDING WALKING:
FREQUENCY/ WEEK 0 1 2 3 4 5 6 7 8 9 10
DURATION (MINS) 10 20 30 40 50 60 70 80 90
TYPES OF EXERCISE
DETAILS……..

ON EXAMINATION

HEART SOUNDS/JVP PULSE……..

LUNGS/ LEGS BP……

ABDOMEN SATS……

SPEECH AND SWALLOW ASSESSMENTS

UNPREDICTABLE SENTENCES

RECORDED YES NO

Practice: Do many magazines these days have long stories

Insert unique 5 McHenry Parle unpredictable sentences

Will you leave the ravioli in the oven.

SUSTAINED VOWEL

MAXIMUM……..DECIBELS
DURATION……SECONDS

150ML WATER SWALLOW

COMPLETED YES NO
DURATION……SECONDS
SWALLOWS……..NUMBER
PAUSES……..NUMBER

ACCELEROMETER

ON YES NO
NUMBER

SWALLOW DETECTION

ON YES NO

BLOODS

BLOOD TEST	DATE TAKEN/ N/A
CBG	
FBC	
BDNF GENOTYPE	
BASELINE BDNF LEVEL	
BDNF PRE EXERCISE 1	
BDNF POST EXERCISE 1	
BDNF PRE EXERCISE 2	
BDNF PRE EXERCISE 2	

GROUP 1 – VISIT 1 CBG/FBC/GENOTYPE/BDNF LEVEL
GROUP 2 – VISIT 1 CBG HLC – FBC/BDNFX2

CBG RESULT

Appendix D. Additional work resulting from thesis and ongoing analyses

Physical Activity; Accelerometer data

Physical activity in research settings has traditionally been quantified using subjective measures, such as questionnaires, these are open to bias and often unreliable. Accelerometry has become an accepted method of objectively quantifying physical activity levels, but minimal studies have used this method to measure the effects of exercise interventions. Accelerometers are motion sensors that can objectively measure movement by measuring acceleration along reference axes and across three planes. Accelerometer outputs are usually expressed in units referred to as 'counts'. Different processing algorithms and equations for signal processing exist to produce a numerical figure to represent the accelerometer output and hence physical activity.
In the RCT arm of the study, participants in both the control and intervention groups wore two personal GeneActiv tri-axial capacitive accelerometers (one on each wrist) for 48 hours at baseline and then again after the 12 week control period or intervention respectively to measure the effects of a twelve week exercise intervention on physical activity levels. The equation used for signal processing was that described by van Hees et al, termed Euclidean norm minus one (ENMO) which resulted in a numerical output unit (ENMO) which reflected physical activity (van Hees et al., 2013). Although not reaching statistical significance, the ENMO data for the intervention group showed a trend towards higher activity after the intervention. In the control group, activity levels based on ENMO did not increase.

Brain Derived Neurotrophic Factor

Exercise is known to provoke a surge of molecular and cellular processes that support brain plasticity. Activity dependent neuroplasticity is supported by neurotrophins, which have the ability to signal neurons to survive, differentiate and grow (Hennigan et al., 2007, Johnston, 2009, Neeper et al., 1995, Neeper et al., 1996, Vaynman and Gomez-Pinilla, 2005). Brain derived neurotrophic factor (BDNF) seems to be the most susceptible neurotrophin to regulation by

exercise (Johnston, 2009, Neeper et al., 1995, Vaynman and Gomez-Pinilla, 2005). Studies have shown decreased BDNF expression within the substantia nigra of PD brains as compared to controls (Howells et al., 2000, Parain et al., 1999).

Part of this study aimed to evaluate the impact of an acute episode of exercise on BDNF levels and the effect of 12 weeks of exercise training on BDNF levels in PD. In the RCT arm of the study, blood was taken for BDNF levels in the control group at baseline and after 12 weeks and in the intervention group immediately before and after the 1st exercise intervention in week 1 and immediately before and after the final exercise intervention in week 12. Plasma samples were assayed for BDNF levels using a commercially available sandwich ELISA kit from Promega (Sweden) according to the manufacturer's instructions.

While analysis of BDNF results is ongoing, the BDNF levels appear to vary notably from one analysis to the next and provisional results indicate there was no difference in the control group from start to finish. In the intervention group there was no significant difference from the start to the end of the 1st or 12th session or when comparing the start of session samples at week 1 and week 12 or the end of session samples at week 1 and week 12.

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